A COMPARATIVE STUDY TO ASSESS COGNITIVE IMPAIRMENT AMONG NATURAL AND SYNTHETIC OPIOID USERS

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Dedicated

to

my Parents

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"Your work is going to fill a large part of your life, and the only way to be truly satisfied is to do what you believe is great work. And the only way to do great work is to love what you do." **Steve Jobs**

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LIST OF ABBREVIATIONS

AIIMS	ALL INDIA INSTITUTE OF MEDICAL SCIENCES
AVLT-R	REY AUDITORY VERBAL LEARNING TEST-RECOGNITION TEST
BGT	BENDER GESTALT TEST
BVMT-R	BRIEF VISUOSPATIAL MEMORY TEST-REVISED
COWA	CONTROLLED ORAL WORD ASSOCIATION TEST
DA	DOPAMINE
DBT	DIGIT BACKWARD TEST
DFT	DIGIT FORWARD TEST
DOP	DELTA RECEPTOR
DSST	DIGIT SYMBOL SUBSTITUTION TEST
DTI	DIFFUSION TENSOR IMAGING
DVT	DIGIT VIGILANCE TEST
ES	EFFECT SIZE
HCV	HEPATITIS C VIRUS
HIV	HUMAN IMMUNODEFICIENCY VIRUS
IGT	IOWA GAMBLING TEST
KOP	KAPPA RECEPTOR
LC	LOCUS COERULEUS
MASH	MIAMI ADULT STUDIES ON HIV
MMSE	MINI-MENTAL STATE EXAMINATION
MOCA	MONTREAL COGNITIVE ASSESSMENT

MOP	MU OPIOID RECEPTOR
MRI	MAGNETIC RESONANCE IMAGING
NA	NORADRENALINE
NAC	NUCLEUS ACCUMBENS
nAChR	NICOTINE ACETYLCHOLINE RECEPTORS
NBT	VERBAL AND VISUAL N-BACK TEST
NBT	NAHOR BENSON TEST
NDDTC	NATIONAL DRUG DEPENDENCE TREATMENT CENTRE
NMPOU	NON-MEDICAL PRESCRIPTION OPIOID USE
NOP	NOVEL RECEPTOR
OUD	OPIOID USE DISORDER
OUQ	OPIUM USE QUANTITY
PFC	PREFRONTAL CORTEX
PLWH	PEOPLE LIVING WITH HIV
PODS	PUNJAB OPIOID DEPENDENCE SURVEY
PODS	PUNJAB OPIOID DEPENDENCE SURVEY
PQ	PERFORMANCE QUOTIENT
RAVLT	REY'S AUDITORY VERBAL LEARNING TEST
SPYM	SOCIETY FOR PROMOTION OF YOUTH AND MASSES
SUD	SUBSTANCE USE DISORDER
TMT	TRAIL MAKING TESTS
TQ	TEST QUOTIENT
UNODC	UNITED NATIONS OFFICE ON DRUGS AND CRIME

VTA	VENTRAL TEGMENTAL AREA
WAIS	WECHSLER ADULT INTELLIGENCE SCALE
WAIS-R	WECHSLER ADULT INTELLIGENCE SCALE REVISED
WCST	WISCONSIN CARD SORTING TEST
WHO	WORLD HEALTH ORGANIZATION
WMS-R	WECHSLER MEMORY SCALE-REVISED

ABSTRACT

Introduction: Opioid Dependence is the major contributor to the global disease burden leading to cognitive impairment in opioid users. Due to the growing use of opioids among the youth, it is necessary to assess the effects of opioids on cognition. A cross-sectional study was performed which compared the cognitive impairment occurring in patients consuming natural and synthetic opioid users.

Aim of Study: To study the effects of opioids on cognitive functions and compare the cognitive impairment between natural and synthetic opioid users.

Materials & methods: The study was conducted on patients in the age group between 18-60 years diagnosed with opioid dependence as per ICD-11 criteria presenting to Deaddiction IPD/Deaddiction OPD, Department of Psychiatry, DMC&H Ludhiana for one year. Cognitive assessment of patients was done using PGIBBD.

Results: A higher dysfunction rating score was seen in the opioid users, particularly in the synthetic opioid users as compared to natural opioid users with p= 0.003 having a medium effect size with Cohen's d of 0.51. Synthetic opioid users exhibited pronounced impairment across various cognitive domains, particularly in executive functioning, memory retention, and perceptual-motor skills. Significant correlations were identified between age, age of onset, duration, and dose of substance use, as well as with various cognitive variables. These correlations varied depending on the type of substance used.

Conclusion: Opioid users, particularly those using synthetic opioids, experienced significant cognitive dysfunction compared to natural opioid users. This dysfunction manifests as impaired judgment, reduced cognitive flexibility, and compromised decision-making abilities, contributing to poorer treatment compliance and outcomes.

Keywords: Cognitive functions, Opioid dependence, Natural opioids, Synthetic opioids, PGIBBD

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INTRODUCTION

Substance use disorder (SUD) is characterised by an inability to manage the consumption of legal or illegal drugs or medications. This condition often starts with recreational drug use in social contexts or through prescribed medication. Over time, individuals may require increasingly larger doses to achieve hedonism, eventually needing the substance to experience euphoria and in the long term to avoid withdrawal symptoms. Efforts to stop using the drug frequently result in withdrawal symptoms, which comprise physical or mental signs such as anxiety, irritability, fatigue, depression, difficulty concentrating, and mood disturbances [1,2].

Opioids are one of the most commonly used substances that have been part of human existence for thousands of years. Disorders due to the use of opioids are a most significant community health concern, associated with substantial health, social, and economic consequences along with decreased quality of life in both low- and high-income societies [3-5]. The group of opioids are analgesic agents that are mined directly from the poppy plant (Papaver somniferum). Opioids are classified according to their mode of synthesis into Natural (Morphine, Codeine, Papaverine) which are the alkaloids derived from the resin of the poppy and Synthetic (Heroin, Buprenorphine, Oxycodone, Tramadol, Tapentadol, Fentanyl) which are chemically synthesised from the natural alkaloids of opium. All opioids have a similar core structure, affecting the same receptors in the brain and the body, exerting a bimodal action, that is, inducing an excitatory action at lower doses and an inhibitory action at higher doses [6]. They act on the 3 classical opioid receptors in the body namely mu receptor/MOP, delta receptor/DOP and kappa receptor/KOP with the novel NOP receptor which is considered to be a non-opioid branch of the opioid receptor family. Opioids exert agonist, antagonist and partial agonist action on these receptors. All opioids used in clinical settings primarily act on MOP receptors and also interact with other opioid receptors or different receptor families [7].

Reports indicate a 33% upsurge in the number of drug users globally from 1990 to 2017, reaching approximately 7.7 million people in the world. The United Nations Office on Drugs and Crime (UNODC) reported in 2021 that about 275 million people worldwide use drugs, with over 36 million suffering from drug use disorders. The estimated number of drug users rose from 240 million in 2011 to 296 million in 2021, accounting for 5.8% of the global population aged 15–64, a 23% increase [8].

Opioid dependence is a substantial contributor to the global disease burden [9]. Among countries reporting the leading drugs causing substance use disorders, 31% identified opioids, primarily heroin, as the most problematic [8]. In 2021, an estimated 60 million people engaged in non-medical opioid use, with 31.5 million using opiates, predominantly heroin [8]. The global population of opiate users comprised 75% males and 25% females, whereas non-medical users of pharmaceutical opioids were 53% males and 47% females [8].

India, with nearly 11 million opioid users in 2021, accounted for almost 90% of South Asia's opioid users and 34% of the global total, despite comprising only 18% of the world's population. In the 10–75 age group, opioid use rates in India range from 0.2% to 25.2%, with opioid use disorders between 0.1% and 6.9% [8]. In 2018, 2.1% of Indians aged 10–75, totalling 23 million people, were past-year opioid users [10]. Heroin was the most prevalent opioid, with a past-year prevalence of 1.14%, followed by non-medical pharmaceutical opioids at 0.96%, and opium at 0.52%. [11]

Opioid use in India predominantly affects males, with heroin use particularly concerning in Punjab, a state significantly impacted by Afghan heroin inflow via Pakistan [8]. Among the top 10 states of India Punjab ranked 2nd with 7.2 lakh population who need help for opioid-related problems. However, regarding the percentage of population affected Punjab ranked 6th with 2.8 per cent population [11]. The AIIMS Punjab opioid dependence survey found 837 opioid dependents per 100,000 population or 0.84% of the state's 28 million population [12].

Opioids have analgesic and sedative effects due to their action on MOP receptors, therefore, are often used for the management of pain. Opioids can cause a reduction in consciousness and result in euphoria, which is one of the central reasons for their non-medical use. Regular non-medical use, prolonged use, misuse, and unsupervised use of opioids can lead to opioid dependence and various health issues. Opioid dependence is a disorder characterised by the inability to regulate opioid use due to repeated or continuous consumption [13].

To make the diagnosis of Opioid dependence, the patient must fulfil the diagnostic criteria as per the International Classification of Disease Edition 11[14]

For a diagnosis, there must be a pattern of recurrent episodic or continuous use of a psychoactive substance, accompanied by evidence of impaired regulation of use, demonstrated by two or more specific criteria:

- Impaired control over opioid use
- Increasing precedence of opioid use over other life aspects: This includes health maintenance and daily responsibilities, with substance use continuing or escalating despite harm or negative consequences.
- Physiological indicators of neuroadaptation: These include tolerance to the opioid's effects, requiring higher amounts to achieve the same effect, withdrawal symptoms upon cessation or reduction, or repeated use of the opioid or similar substances to prevent or relieve withdrawal symptoms.
- Duration of dependence: Typically, evident over at least 12 months, but a diagnosis can be made if use is continuous (daily or nearly daily) for at least three months.

These criteria highlight the significant impact of opioid dependence on an individual's health and daily functioning.

Cognitive control is essential for behavioural learning and adaptation in a dynamic environment. Cognitive functions encompass executive functions,

attention, memory, and visual-spatial skills [15]. They also include imagination, learning, decision-making, and conscience [15,16]. Cognitive control processes, such as response inhibition, error detection, and post-error adjustment, are compromised in individuals with addiction. Developing new skills to prevent relapse, managing impulsive responses and automatic thoughts, and formulating problem-solving strategies are crucial for adapting to a new lifestyle and avoiding substance use.

Opioid use disorders are linked with impairments in cognitive and affective functions, as determined by neuropsychological assessments and brain imaging studies. The cognitive effects of opioids are primarily due to their action on mu-opioid receptors in limbic and cortical areas [17]. While acute opioid intake can temporarily impair some cognitive functions, these effects do not last long. However, chronic opioid use can lead to long-lasting cognitive deficits, particularly in verbal working memory, cognitive impulsivity (risk-taking), and cognitive flexibility (verbal fluency) [18].

Human cognitive processes involve understanding how individuals acquire information from the environment and utilize their knowledge and experiences. These processes include acquiring sensations, perceptiveness, and attention. Higher-order mental processes used in cognition, such as memory, reasoning, learning, and problem-solving, enable individuals to understand and adapt to their surroundings. Disturbances in cognitive functions indicate various psychopathological changes and are critical for diagnosing disorders [19].

Opioids have been interrelated with numerous neuropsychological impairments during both long-term use as well as after a period of cessation [20]. Neuropsychological studies of chronic opioid users have identified deficits in executive functions, including impairments in decision-making [20], cognitive flexibility [21], strategic planning [22,23], and inhibitory control [24]. These cognitive impairments adversely impact functionality, quality of life, treatment adherence, and outcomes.

Cognitive maladaptation refers to neuroadaptations resulting from the heightened salience of drug rewards. Examples include heightened sensitivity to short-term rewards and increased attention to drug-related cues, which could potentially be mitigated through cognitive techniques [25]. Chronic heroin use leads to neuroadaptations that extend beyond reward circuits, affecting other brain systems involved in cognition and stress responses [26]. Key brain regions impacted include the amygdala, hippocampus, and cerebral cortex, and their connections to the nucleus accumbens.

Opioids also impact the respiratory system by reducing the respiratory rate and suppressing airway reflexes, which is beneficial during anaesthesia [7]. While opioids are known to maintain cardiac stability, morphine can cause histamine release, leading to decreased systemic vascular resistance and blood pressure. Other side effects of opioids include constipation, nausea, vomiting, urinary retention, pruritus, muscular rigidity, miosis, and dysphoria [7]. In cases of overdose, opioids can be fatal. According to the WHO, more than 70% of the approximately 500,000 drug-related deaths are due to opioids [10].

Research on cognitive functions in opioid addicts is limited. Before opioid use, individuals often consume gateway drugs for extended periods, with heroin typically being the final substance used. The number of studies examining the impact of opioids is limited [27-29]. Existing studies indicate that individuals with opioid dependence exhibit diminished brain functions compared to normal subjects, particularly in executive functions such as planning, impulse control, memory processing, and decision-making [23,30,31]. While some studies suggest that cognitive impairment persists in opioid-dependent individuals, others argue that the impairments are due to the toxic effects of the substance and that cognitive functions can normalise after cessation of use [20,24,32,33]. The procedural characteristics of existing studies limit the generalizability of the results.

As per the knowledge of the investigator, very few studies have been conducted in Indian scenarios comparing the impact of opioids on cognition as well as the studies that compared the two groups of opioids and their effect on cognition. Thus, in this study, we examined the potential link between opioid use and cognitive impairment. The comparison was done in terms of cognitive impairment between natural and synthetic opioid users. The findings of the study would help to formulate treatment strategies to improve quality of life, enhance functionality, treatment compliance and prevention of relapses.

AIMS AND OBJECTIVES

1. To study the effects of opioids on cognitive functions.

2. To compare the cognitive impairment among the groups- natural and synthetic opioid users

REVIEW OF LITERATURE

Opioid use disorder (OUD) is characterized by the chronic consumption of opioids, leading to significant distress or impairment. Symptoms include a strong urge to use opioids, increased tolerance, and withdrawal symptoms upon cessation. OUD encompasses a spectrum from harmful use to full dependence and affects over 16 million people globally. In the United States, the number of individuals regularly using opioids is comparable to those diagnosed with obsessive-compulsive disorder, psoriatic arthritis, and epilepsy. Annually, more than 120,000 deaths worldwide are attributed to opioids.

The increasing prevalence of OUD and related fatalities underscores the need for clinicians to understand its complexities. OUD often involves cycles of exacerbation and remission, with a persistent risk of relapse throughout a patient's life. Stressful events, economic instability, and relationship problems can heighten this risk. Similar to other chronic relapsing conditions, OUD can present severe symptoms and challenges in treatment adherence.

The development of opioid use and dependence results from a mix of biological, environmental, genetic, and psychosocial factors. While most opioids are prescribed by physicians, many are also acquired illegally. Even after a short duration of use, patients may develop dependence, manifesting as physical, psychological, or both. Abrupt cessation leads to withdrawal, prompting many to continue using opioids, legally or otherwise, to avoid these symptoms.

Patients particularly at risk for OUD include those with neurotransmitter deficiencies like dopamine or those with first-degree relatives with substance use disorders. Environmental exposure, such as peer opioid use or prior exposure to opioid analgesics, also increases risk. Additionally, individuals with untreated depression, post-traumatic stress disorder, a history of sexual abuse, anxiety, or childhood trauma are at heightened risk for developing OUD.

The prevalence of opioid use and dependence differs by age and gender. Men are more prone to opioid use and dependency, with more than 95% of opioid users in India being men, who have a prevalence rate of 4%, compared to 0.2% among women [11]. Consequently, men represent the majority of opioid-related overdoses. Women, however, are more frequently prescribed opioids for pain relief than men. The highest rates of opioid-related deaths occur among individuals aged 40 to 50, while heroin overdoses are most common among those aged 20 to 30 [34].

A study by Ajit Avasthi et al. [35] titled "Epidemiology of Substance Abuse and Dependence in the State of Punjab (India)" revealed that 6% of individuals aged 11-60 years in Punjab had experienced substance dependence at some point in their lives. Currently, 1 in 120 people in this demographic is dependent on opioids, with an estimated 0.17 million individuals affected, accounting for 61.6%. Among these, 1 in 4 uses injectable opioids (heroin), and one-third abuses buprenorphine. The primary reasons for initiating opioid use were for fun (69.9%) and peer pressure (43.9%) [12]. According to a survey by All India Institute and SPYM in collaboration with NDDTC AIIMS, Punjab has approximately 2.32 lakh opioid users. The Population Opioid Dependence Study (PODS) [36] found 837 opioid dependents per 100,000 people in Punjab, equating to 0.84% of the state's 28 million population. Among these, 76% were aged 18-35 years [37], with 53% using heroin, 33% using opium/doda/phukki, and 14% using pharmaceutical opioids. Additionally, 29% were injecting drug users, with 90% of them injecting heroin. Peer influence was cited as the reason for starting drug abuse in 75% of cases, 80% attempted to quit, and only 35% ever received help for quitting.

Opioid addiction, the most severe complication of opioid use disorder, occurs by sensitizing the drug-reward system and intensifying compulsive drug-seeking behavior. Chronic opioid use particularly affects the orbitofrontal area, crucial for regulating anxiety, emotional responses, and reward-related behaviours. Opioid addiction impacts all aspects of an

individual's life, leading to legal troubles, loss of personal relationships, and significant morbidity and mortality [38]. Opioid withdrawal, another critical complication, varies in onset depending on the type of opioid. Heroin withdrawal can begin as early as five hours after the last dose, while methadone withdrawal may start 2 to 3 days later. The duration of withdrawal symptoms varies among individuals, lasting from a few days to several weeks [39]. Opioid overdose is another risk associated with opioid use disorder. The risk of overdose remains high in untreated patients, but it is also significant in those undergoing treatment, especially between detoxification and the start of maintenance therapy. Cognitive-behavioural therapy can help reduce this risk, but unfortunately, the mortality rate among patients on chronic opioids remains alarmingly high [40].

Opioids have historically been used for their analgesic properties, acting on opioid receptors in the central and peripheral nervous systems. In the central nervous system, the primary mechanism of opioid-induced analgesia involves the activation of MOP receptors in the midbrain. MOP agonists indirectly activate descending inhibitory pathways by acting on the periaqueductal grey and the nucleus reticularis paragigantocellularis. This activation increases neuronal traffic through the nucleus raphe magnus, leading to enhanced stimulation of neurons containing 5-hydroxytryptamine and enkephalin. These neurons connect directly with the substantia gelatinosa of the dorsal horn, reducing nociceptive transmission from the periphery to the thalamus. Both exogenous and endogenous opioids can also directly inhibit the substantia gelatinosa in the dorsal horn and peripheral nociceptive afferent neurons, thereby diminishing nociceptive transmission from the periphery [7].

The primary cause of opioid dependence is the drug’s effect on the mesolimbic reward system in the midbrain. This reward system stimulates the ventral tegmental area (VTA), leading to the release of dopamine (DA) in the nucleus accumbens (NAc), which induces feelings of pleasure. Various brain regions create lasting memories that associate these

pleasurable feelings with specific circumstances and environments, known as conditioned associations. These associations cause cravings when the user re-encounters those stimuli, driving the compulsion to seek more drugs. In the early stages of abuse, the opioid-induced stimulation of the brain's reward system is a significant factor in repeated drug use [7]. This growing compulsion eventually leads to tolerance and dependence.

Opioid dependence and withdrawal symptoms arise from activity in the locus coeruleus (LC) at the base of the brain. LC neurons produce norepinephrine (NA), which is involved in wakefulness, respiration, blood pressure, and general alertness. When opioids bind to MOP receptors in the LC, they suppress NA release, resulting in drowsiness, slowed respiration, and low blood pressure—effects characteristic of opioid intoxication. However, with repeated opioid exposure, LC neurons adapt by increasing their activity. Consequently, when opioids are present, their suppressive effect is counterbalanced, leading to nearly normal NA release and a relatively normal state for the individual. In the absence of opioids, the overactive LC neurons release excessive amounts of NA, causing symptoms such as jitters, anxiety, muscle cramps, and diarrhoea.

Disorders resulting from opioid use develop along a continuum. The physical dependence on opioids can develop rapidly, attributed to various changes in mu-opioid receptors, including receptor desensitization, internalization, and signalling abnormalities. This physical dependence causes withdrawal symptoms when opioid use is abruptly discontinued, creating both positive and negative reinforcement for continued use. Patients diagnosed with opioid use disorders report significant impairment or distress, often stemming from an inability to control opioid use and intense cravings.

Prolonged opioid use significantly impacts cognitive processes. The cognitive deficits model of drug addiction suggests that individuals with addictive disorders have abnormalities in the prefrontal cortex (PFC), which is crucial for judgment, planning, and other executive functions. The

PFC sends inhibitory signals to the ventral tegmental area (VTA) dopamine neurons in the mesolimbic reward system, helping to curb impulses for immediate gratification in favour of long-term rewards [41].

The model posits that in individuals with addictive disorders, PFC signalling to the mesolimbic reward system is impaired, leading to a decreased ability to use judgment to control impulses, resulting in compulsive drug-taking behaviours [15]. Stimulants like methamphetamine damage the frontostriatal loop, the brain circuit responsible for transmitting inhibitory signals from the PFC to the mesolimbic reward system. The cognitive deficits model may explain clinical observations that heroin dependence is more severe in individuals with antisocial personality disorder, a condition independently associated with PFC deficits [42]. While heroin damages the PFC, it does not affect the frontostriatal loop. Therefore, individuals who become dependent on heroin may have preexisting PFC damage, either genetically inherited or caused by other factors, predisposing them to impulsivity and lack of control. Chronic heroin use exacerbates this PFC damage, worsening these issues [43].

Pekka Rapeli et al. [44] (2006) conducted a study on cognitive function during early abstinence from opioid dependence. The study involved fifteen opioid-dependent patients and fifteen control participants matched for age, gender, and verbal intelligence. The participants were assessed using a cognitive test battery. The results showed that early abstinent opioid-dependent patients performed significantly worse than controls on tests measuring complex working memory, executive function, and fluid intelligence. Significant correlations were found between complex working memory and fluid intelligence performance with the number of days of withdrawal. The study concluded that early abstinence from opioid dependence is associated with a general neurocognitive deficit in higher-order cognition, likely due to withdrawal-induced neural dysregulation in the prefrontal cortex, which appears to be transient.

A. Baldacchinoa et al. [18] (2012) conducted a quantitative review and meta-analysis on the neuropsychological consequences of chronic opioid use. This review followed the MOOSE (meta-analysis of observational studies in epidemiology) [45] and PRISMA (preferred reporting items for systematic reviews and meta-analysis) [46] guidelines. The meta-analysis suggested that chronic opioid use is linked to deficits across various neuropsychological domains. However, significant impairments were primarily found in verbal working memory, cognitive impulsivity (risk-taking), and cognitive flexibility (verbal fluency). According to Cohen's benchmark criteria [47], the effect sizes in these cognitive domains were medium. The analysis also highlighted methodological issues in the existing literature and underscored the importance of meta-analytic techniques in elucidating the neuropsychological consequences of chronic opioid use from core addiction phenotypes.

Scott C. Wollman et al [48] 2018 conducted a research synthesis and meta-analysis on Neuropsychological functioning in opioid use disorder. Articles comparing patients with opioid use disorder to healthy controls were selected. In total, 61 articles studied were selected for the analyses. These comprised two thousand five hundred eighty patients with opioid use disorder and two thousand one hundred and two healthy control participants. Drug-related variables were analyzed as potential moderators. Results showed that the largest effect size difference in neuropsychological performance was seen in complex psychomotor ability. Except for the motor and speed processing domains, which showed no group differences, small-to-medium effect sizes were associated with all neurocognitive domains assessed. Meta-regression revealed that as the period of abstinence increased, there was a decrease in effect sizes of the complex psychomotor domain. In addition to this, attentional ability predicted effect size differences in executive functioning as well as verbal memory ability. Although the majority of meta-analyzed studies demonstrated significant differences between patients with opioid

use disorder and controls, the average raw scores for patients with opioid use disorder in these studies typically fell within the normal range. The authors concluded that the pattern of neuropsychological performance amongst patients with opioid use disorder seems to reflect mild generalized cognitive dysfunction, with a large effect on complex psychomotor abilities.

Sara L. Kroll et al [49] 2018 A study on the cognitive and socio-cognitive functioning of chronic non-medical prescription opioid users assessed 23 individuals confirmed by hair analysis and 29 opioid-naïve controls using a comprehensive neuropsychological test battery. The results showed significant impairments in attention ($p < .01$, Hedge's $g = .85$), declarative memory ($p < .05$, $g = .66$), and global cognitive empathy ($p < .01$, $g = 0.99$) in the NMPOU group compared to controls. Opioid hair concentrations, converted to morphine equivalents, negatively correlated with global cognitive empathy ($r = -0.52$, $p < .01$), indicating dose-dependent deficits. The authors concluded that NMPOU individuals exhibit selective impairments in cognitive empathy, with potential opioid-induced deficits and the involvement of the opioid system in these processes. These findings have significant implications for interventions focusing on social functioning to enhance therapy outcomes and prevent relapse.

Buket Koparal et al. [50] (2019) examined cognitive functions in opioid-dependent males based on the duration of abstinence. Conducted at Gazi University Medical Faculty, the study included 96 males undergoing maintenance treatment post-detoxification, divided into three groups based on abstinence duration. Using the Wisconsin Card Sorting Test, Rey Auditory-Verbal Learning Test, and Stroop Test, the results indicated no significant cognitive impairment compared to norm values. However, patients with 0-3 months of abstinence had higher memory scores than those abstinent for over a year. The study identified factors such as the duration of multiple substance use, age of first substance use, and number of treatments as negatively affecting some cognitive functions.

The authors noted this study as the first to assess cognitive functions in opioid-dependent males in Turkey, acknowledging the difficulty in controlling all factors influencing cognitive functions.

Rajoo Saroj et al. [51] (2020) conducted a comparative study on neurocognitive functions in patients on buprenorphine maintenance for opioid dependence, with three matched control groups. The groups were matched for age, sex, and education years, including a healthy control group (30 participants) and two other comparison groups (20 participants each). Cognitive assessments included TMT-A & B, DVT, NBT, RAVLT, WCST, COWA, and WAIS. The buprenorphine group performed significantly worse in TMT-B, verbal NBT, DVT, and WCST compared to controls. Even when controlling for IQ, significant differences persisted in TMT-B, indicating poor cognitive flexibility. The detoxified group showed poorer performance than both the naltrexone and control groups in several tests. The study concluded that medication-assisted treatment patients exhibit significant cognitive impairments, though the severity was highest in the actively opioid-dependent group.

Elnaz Gharahi et al. [52] (2021) conducted a study on cognitive network reconstruction in opioid users compared to non-users, employing topological analysis through graph models and centrality measures. The researchers administered n-back, selective and divided attention, and Wisconsin Card Sorting tests, then reconstructed the interactive cognitive network of subscales or domains for both groups. The analysis aimed to identify the most central cognitive functions and their connections. Each network was evaluated based on the betweenness and closeness centrality measures. Results showed that in the opioid users' network, the reaction time and number of commission errors were the most central subscales in the divided attention module. In contrast, the number of correct responses and commission errors were central in non-users. These findings indicated that opioid users have impaired divided attention, as evidenced by higher reaction times and errors. The study suggests that

targeting divided attention in cognitive therapies and rehabilitation could enhance overall cognitive performance.

Travis M. Scott et al. [53] (2021) studied the neurocognitive, psychiatric, and substance use characteristics in a diverse sample of individuals with opioid use disorder who began treatment with methadone or buprenorphine/naloxone. Ninety-seven adults with OUD participated in a randomized longitudinal trial comparing the effects of these treatments on neurocognitive functioning. Participants completed comprehensive evaluations of neurocognitive, psychiatric, and substance use characteristics within one week of starting treatment. The results showed that a significant portion of the sample met the criteria for learning (79%) and memory (69%) impairments. Additionally, half of the participants exhibited symptoms of depression, and comorbid substance use was prevalent. Lifetime cannabis and cocaine use disorders were associated with better neurocognitive functioning, while depression was linked to worse neurocognitive outcomes. The authors concluded that learning and memory impairments are highly prevalent in individuals with OUD starting treatment with either methadone or buprenorphine/naloxone in opioid treatment programs.

Hilde Hoel Fjærli et al. [54] (2021) conducted a study comparing cognitive recovery in psychostimulant users and opioid users, measured with the Montreal Cognitive Assessment (MoCA®). The study included 91 patients with MoCA® scores taken at admission and before discharge from long-term treatment, with two subgroups of 21 participants each. Results showed that MoCA® sum scores were statistically similar between the groups at both admission and discharge. However, within the opioid user group, there was a significant improvement in MoCA® sum scores from admission to discharge, unlike the psychostimulant group. The authors concluded that their data suggest differences in cognitive recovery between psychostimulant and opioid users, indicating a need for focused

cognitive function assessments and possibly tailored treatment content for psychostimulant users.

Hossein Sanjari Moghaddam et al. [55] (2021) assessed cognitive impairment in opioid use disorder in a cross-sectional study. Thirty outpatients with opioid use disorder and 20 healthy controls were evaluated using a neuropsychological battery including the Auditory Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Digit Forward and Backward Tests, WAIS-R and Digit Symbol Substitution Test. The study found that the most affected cognitive functions in opioid use disorder patients were working memory and information-processing speed, as measured by the Digit Backward Test and Digit Symbol Substitution Test. No significant differences were found based on the route of administration. Scores on the Digit Backward Test correlated with opium use quantity and the duration of use, indicating that these tests can be effective in clinical settings for assessing cognitive deficits in opioid use disorder patients.

Javier A. Tamargo et al. [56] (2021) published findings from the Miami Adult Studies on HIV (MASH) cohort on cognitive impairment among heroin and fentanyl users. The study included 265 people living with HIV (PLWH) and 284 HIV-uninfected participants, with 26.8% of PLWH and 15.1% of the HIV-uninfected using opioids. Cognitive impairment was measured using the Mini-Mental State Examination (MMSE). The study found that cognition was more significantly impaired among heroin and fentanyl users compared to those misusing prescription opioids (31.6% vs. 10.5%, p=0.005). Heroin/fentanyl use was associated with increased odds of cognitive impairment (adjusted OR: 2.21, 95% CI 1.05–4.64, p=0.036). Among PLWH, opioid use was linked to more neuropsychiatric symptoms, including depression and apathy, highlighting a higher risk for cognitive impairment among heroin and fentanyl users.

Abhishek Ghosh et al. [57] (2022) investigated the relationship between neurocognition and treatment retention in subjects on opioid agonist

treatment, involving 56 subjects aged 18 to 45 years, registered between March and December 2017. During the first week of treatment, executive function, decision-making, attention, psychomotor speed, and working memory were assessed using the WCST, IGT, Trail Making, and verbal and visual N-back tests. Treatment retention was reassessed after 12 weeks. Results showed that the mean age of the subjects was 26 (±5.9) years, and 50% of the subjects remained in treatment. Neurocognitive functions at the start of treatment did not differ significantly between those who remained in treatment and those who dropped out. However, higher severity and shorter duration of dependence and use were related to higher treatment discontinuation. A regression model incorporating cognitive functions and significant clinical variables explained 38% of the variance in treatment retention.

Yang Tian et al. [58] (2022) studied cognitive deficits in patients with methamphetamine and heroin use disorder compared to healthy controls in a Chinese Han population. The study included 567 methamphetamine patients, 78 heroin patients, and 201 healthy volunteers, assessing cognitive functions using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Results showed that both methamphetamine and heroin users performed significantly worse than controls on all RBANS subtests and total scores (all $p<0.05$). Methamphetamine users exhibited more severe delayed memory impairment than heroin users ($p=0.02$). Additionally, drug-related factors such as duration of abstinence, age of first use, and duration of use were significantly associated with memory and visuospatial/constructional indices in methamphetamine users (all $p<0.05$), whereas no such associations were found in heroin users (all $p>0.05$).

Nafisseh S. Warner et al. [59] (2022) conducted a population-based observational study on the impact of prescription opioids and longitudinal changes in cognitive function in older adults. The study, part of the Mayo Clinic Study of Aging, included 4218 participants with a median age of 76

years. Over a median follow-up of 7.5 years, 2977 participants received at least one opioid prescription. Results indicated a small but statistically significant decline in global cognitive function (−0.007 per opioid prescription; $p<0.001$), particularly in memory, language, and attention domains. Opioid prescriptions were associated with a small but statistically significant decline in long-term cognitive function reflecting an increased incidence of mild cognitive impairment.

Abhishek Ghosh et al. [60] (2023) examined neurocognitive functions in individuals dependent on different opioid categories, including heroin (n=120), pharmaceutical opioids (n=52), and natural opioids (n=66), compared to healthy controls (n=94). The study found that the pharmaceutical opioid group exhibited worse performance on the Wisconsin Card Sorting Test and higher error scores on verbal and visual N-Back Tests than healthy controls. Both the pharmaceutical and heroin groups performed worse than the natural opioid group on visual N-Back Tests. The pharmaceutical opioid group showed the most significant cognitive impairments, while cognitive functions were relatively preserved in the natural opioid group.

In another study by Abhishek Ghosh et al. [61] (2023), the neurocognitive functions of patients with comorbid hepatitis C (HCV) and opioid dependence were compared. The study included 40 HCV-positive and 40 HCV-negative opioid-dependent individuals. Results revealed that the HCV-positive group performed significantly worse on the Standard Progressive Matrices and exhibited more errors on the verbal N-Back Tests than the HCV-negative group and healthy controls. Both HCV-positive and HCV-negative groups performed worse than controls on the Iowa Gambling Task and visual N-Back Tests, with more pronounced deficits in the HCV-positive group. The findings suggest that chronic HCV infection exacerbates cognitive impairments in opioid-dependent individuals, particularly in decision-making and visual working memory.

Ornstein et al. [30] (2000) conducted a study comparing groups of subjects whose primary drug of abuse was either amphetamine or heroin, alongside age and IQ-matched control subjects. The assessment involved a neuropsychological test battery, including both conventional and computerized tests, evaluating recognition memory, spatial working memory, planning, sequence generation, visual discrimination learning, and attentional set-shifting. The study profiled cognitive dysfunction in 22 men who had regularly used opiates, mainly heroin, for at least three years and met the diagnostic criteria for opioid dependence. Heroin users showed impairments in learning the typically easier intra-dimensional shift component, verbal fluency learning, spatial working memory, strategic performance, and visual pattern recognition. The group using heroin did not demonstrate a notable improvement between the two segments of a sequence generation task following training. Moreover, they displayed increased perseverative behaviour during the task. These findings suggest that chronic drug use may lead to distinct cognitive impairment patterns associated with dysfunction in different components of the cortico-striatal circuitry.

Bruijnen et al. [62] (2019) conducted a study in the Netherlands to estimate the prevalence of cognitive impairments using the Montreal Cognitive Assessment among 656 patients with substance use disorder, including 391 alcohol users, 123 cannabis users, 100 stimulant users, and 26 opioid users. The overall prevalence of cognitive impairments was 31%, with specific rates of 34% for alcohol, 38% for opioids, 21% for cannabis, and 27% for stimulants. Opioid users performed significantly worse on tests of visuospatial abilities and memory function, with a notable impact on executive functioning. Younger patients scored higher than older ones.

Bassiony et al. [63] (2017) estimated the prevalence and correlates of cognitive impairment among tramadol-abuse patients and control subjects, including 100 tramadol-abuse patients and 100 control subjects. Participants were assessed using the Montreal Cognitive Assessment test

and urine drug screenings. The study found that 24% of cases used tramadol alone, while the rest used tramadol alongside other substances, mainly cannabis (66%) and benzodiazepines (27%). Tramadol-abuse patients were about three times more likely to have cognitive impairment than control subjects (81% vs. 28%). Those using tramadol alone were more than twice as likely to have cognitive impairment compared to controls (67% vs. 28%). A significant association was found between cognitive impairment and polysubstance abuse, with no links to sociodemographic or clinical factors. The most affected cognitive domains included memory, visuospatial skills, and verbal fluency.

MATERIALS AND METHODS

SOURCE OF DATA

The study was conducted on patients diagnosed with Opioid Dependence who presented to Deaddiction IPD/Deaddiction OPD, Department of Psychiatry, Dayanand Medical College & Hospital, Ludhiana

METHOD OF COLLECTION OF DATA

Sample collection: A comparative and cross-sectional study was performed on patients seeking treatment for Opioid Dependence who presented to Deaddiction IPD/Deaddiction OPD, Department of Psychiatry, Dayanand Medical College & Hospital, Ludhiana during 1 year with the patient group divided into 2: one group who used natural opioids and a second group who used synthetic opioids.

Patients

Inclusion criteria

1. Participants fulfilling Opioid Dependence Criteria as per ICD-11.
2. Using opioids for a minimum period of 12 months.
3. Age between 18-60 years.
4. Willing to give informed consent for participation.

Exclusion criteria

1. Intellectual disability, major psychiatric illnesses, neurological illness or head injury that limit the validity of cognitive tests.
2. Meeting criteria for use of other substances (excluding nicotine).

To avoid additional bias, participants who reported using opioids as prescribed by the physician were not included in this analysis.

Methodology

The study was conducted on patients in the age group of 18-60 years diagnosed with Opioid Dependence presenting to Deaddiction IPD/Deaddiction OPD, Department of Psychiatry, DMC&H, Ludhiana during one year with one group of patients using natural opioids and another group using synthetic opioids. Eligible patients fulfilled the inclusion criteria and gave written informed consent before enrollment.

Their cognitive function was assessed using the following neuropsychological assessment test.

Instrument

A validated cognitive instrument, the PGIBBD (Post Graduate Institute Battery of Brain Dysfunction), was administered. This test battery assesses all cognitive domains and aims to create a psychometric profile that can distinguish patients with organic brain dysfunction from those without. Developed by Pershad and Verma in 1990, it measures cognitive functions such as intelligence (verbal and performance), memory, perceptual acuity, and inter-hemispheric transfer. It focuses on the reception, consolidation, and execution of stimuli, without targeting brain pathology lateralisation or localisation of hemispheric functions. The battery includes the PGI-Memory Scale, Battery of Performance Tests of Intelligence, Verbal Adult Intelligence Scale, Nahor-Benson Test, and Bender Visual-Motor Gestalt Test, taking about 90 to 120 minutes to complete.

A. PGI-Memory Scale (PGIMS): This scale encompasses both verbal and non-verbal elements and assesses various memory types, including remote, recent, immediate, short-term, very short-term, intermediate-term, and long-term memory. It consists of 10 subtests standardized on adults aged 20 to 45. The test-retest reliability over a week ranges from 0.69 to 0.85 for the subtests and approximately 0.90 for the overall test (both test-retest and split-half reliability). The PGIMS correlates with Boston's Memory Scale and Wechsler's Memory Scale at 0.71 and 0.85, respectively. It shows a high correlation with educational level and a low correlation with IQ. The scale demonstrates satisfactory cross-validity and provides quintile norms and a profile, with separate norms for three educational levels: '0 to 5', '6 to 9', and '10 and above' years of schooling. (Pershad, 1977; Pershad and Wig, 1976, 1988)

B. Revised Bhatia's Short Battery of Performance Tests of Intelligence (SB-R): This is an adaptation of Bhatia's Battery of

Performance Tests of Intelligence (Bhatia, 1955) Short Scale (Murthy, 1966), which includes Koh's Block Design and Alexander's Pass-A-Long tests. This short scale was standardized on healthy adults aged 20-59 years. The scoring system was modified, and norms were developed for four age groups and three educational levels, separately for males and females, to enhance score sensitivity. It provides Test Quotients (TQ) for the two sub-tests, facilitating the comparison of functions measured by Koh's Block Design Test and Pass-A-Long test. The TQs of these tests were found to have significant correlations with the IQs measured by the Verbal Adult Intelligence Scale, Wechsler's Adult Performance Intelligence Scale, and Standard Progressive Matrices. The IQ distribution followed a normal probability curve, with elderly individuals and those with lower education levels scoring significantly lower. (Pershad, Mahajan and Verma, 1988)

C. Verbal Adult Intelligence Scale (VAIS): This Verbal Tests of Intelligence battery consists of four sub-tests: (1) Information, (2) Digit Span, (3) Arithmetic, and (4) Comprehension. The development of these sub-tests was guided by Wechsler's Adult Intelligence Scale. The pass percentages for the items were determined across various educational groups of adult participants. Scores from the sub-tests—information, digit span, arithmetic, and comprehension—and the total score were correlated with Bhatia's Short Scale, Standard Progressive Matrices, Stanford Binet, Wechsler's Performance Scale, and WAIS-R. Generally, scores in all four areas tend to improve with higher levels of education. This battery provides norms for three educational levels and five age groups, with separate norms for males and females. It uses the concept of Test Quotient (TQ) to assess performance levels for each sub-test, with the mean of the four TQs constituting the Verbal Quotient (VQ). Unlike some tests, it emphasizes the power and capacity of the subjects rather than speed or quickness. (Pershad and Verma, 1978)

D. Nahor-Benson Test (NBT): Nahor and Benson (1970) designed a rapid and straightforward screening test for organic brain pathology. To evaluate its screening capacity and validate its utility claims, a retrospective study was conducted at PGIMER, Chandigarh. The study found that individuals diagnosed with brain dysfunction frequently reproduced the drawings incorrectly compared to those without brain dysfunction. Specifically, about 90% of non-brain dysfunction patients made errors on two or fewer drawings, while 75% of brain dysfunction patients made more than two errors. Age was not significantly correlated with the number of errors (r=0.08), but education had a slight, significant negative correlation (r=-0.47). The test errors correlated with the Performance Quotient (PQ) and Verbal Quotient (VQ) at 0.27 and 0.45, respectively. (Pershad and Verma, 1978)

E. Bender Visual Motor Gestalt Test (BVMGT) or Bender Gestalt Test (BGT): Introduced by Bender in 1938, the Bender Gestalt test is based on Wertheimer's seminal work in perception. Surveys conducted in India and other countries have consistently ranked the Bender Gestalt test among the top 10 most frequently used psychological tests, often placing it between the 1st and 5th positions. The test involves nine simple, non-threatening drawings that subjects are required to copy. Errors in reproducing these drawings are more commonly observed in individuals with brain dysfunction compared to those without. Additionally, the orientation of the paper when copying the design has minimal impact on the performance of the subjects. (Verma, 1974)

Interpretation of PGI-BBD: Each test variable is scored as 0,2,3 where 0 indicates no deviation, 2 indicates slight deviation and 3 indicates great deviation from normal. A rating of 0,2,3 gives the sum of ratings of all variables which provides the total dysfunction rating score. The minimum and maximum total dysfunction rating score on psychological test variables ranges from 0 to 57. A cut-off point of 20 was taken for the total dysfunction rating score.

STATISTICAL ANALYSIS

Data will be described using range, mean ± standard deviation (SD), median, frequencies (number of cases), and relative frequencies (percentages) as applicable. To assess the normality of the data distribution, the Kolmogorov-Smirnov test will be utilised. Comparisons of quantitative variables between study groups will be performed using the Student t-test, Mann-Whitney U test, and ANOVA for parametric and non-parametric data, respectively. For categorical data comparisons, the Chi-square ($\chi 2$) test will be conducted, with the Fisher exact test employed when the expected frequency is less than 5. To evaluate correlations, both the Spearman rho and Pearson tests will be applied accordingly. A p-value of less than 0.05 will be considered statistically significant. All statistical analyses will be conducted using SPSS version 21 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows.

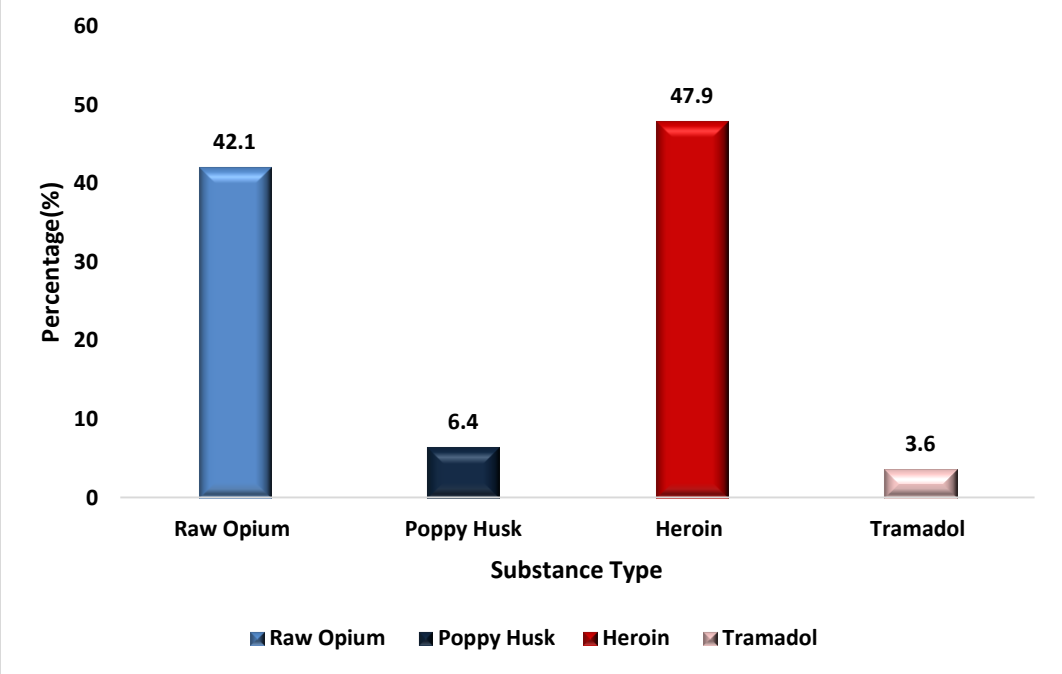
OBSERVATION AND RESULTS

It was a cross-sectional and comparative study that was conducted on patients seeking treatment for Opioid Dependence who presented to Deaddiction IPD/Deaddiction OPD, Department of Psychiatry, Dayanand Medical College & Hospital, Ludhiana during the period of 1 year with the patient group divided into 2: one group who used natural opioids and a second group who used synthetic opioids.

Table 1: Distribution of study subjects according to substance used

Type	Frequency(n)	Percentage (%)
Natural	68	48.6
Raw opium	59	42.1
Poppy husk	9	6.4
Synthetic	72	51.4
Heroin	67	47.9
Tramadol	5	3.6

Figure 1: Bar graph showing distribution of study subjects according to substance used

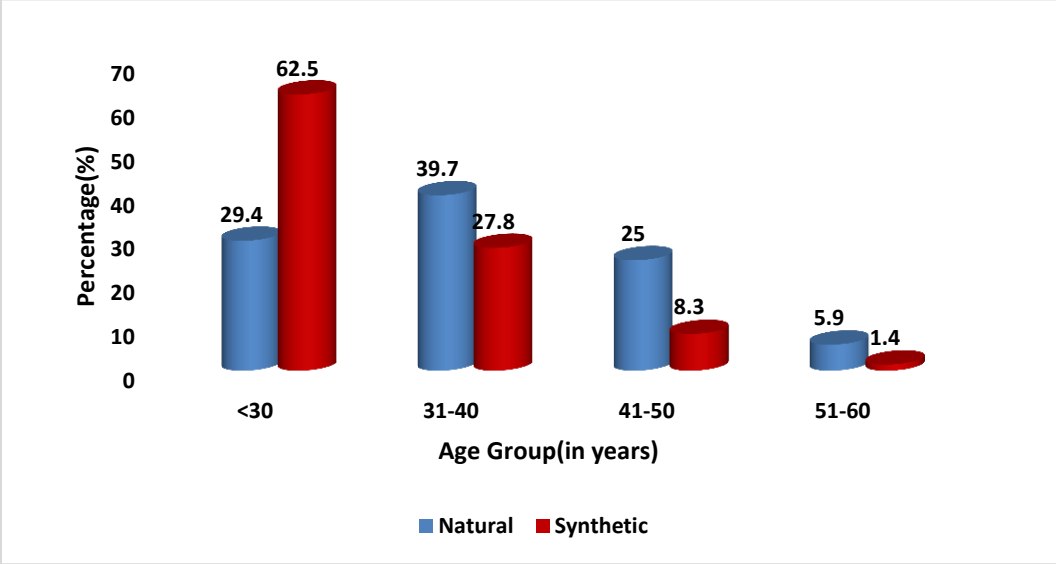


Majority used synthetic opioids, predominantly heroin.

Table 2: Distribution and association of the age group with the type of substance used

Age group (years)	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
<30	20	29.4	45	62.5	65	46.4	17.61	**0.001**
31-40	27	39.7	20	27.8	47	33.6		
41-50	17	25	6	8.3	23	16.4		
51-60	4	5.9	1	1.4	5	3.6		
Total	68	100	72	100	140	100		

Figure 2: Bar graph showing the distribution of the age group with the type of substance used

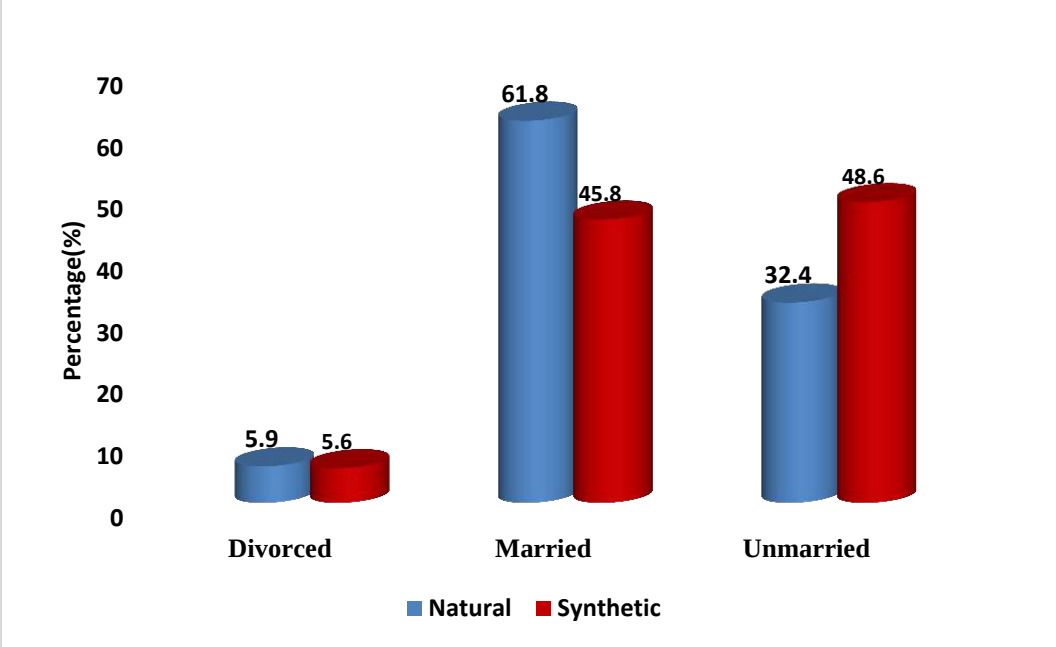


Majority belonged to the younger age group (<30 years), and predominantly used synthetic opioids

Table 3: Distribution and association of marital status with the type of substance used

Marital status	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
Divorced	4	5.9	4	5.6	8	5.7	3.93	0.14
Married	42	61.8	33	45.8	75	53.6		
Unmarried	22	32.4	35	48.6	57	40.7		
Total	68	100	72	100	140	100		

Figure 3: Bar graph showing distribution of marital status with the type of substance used

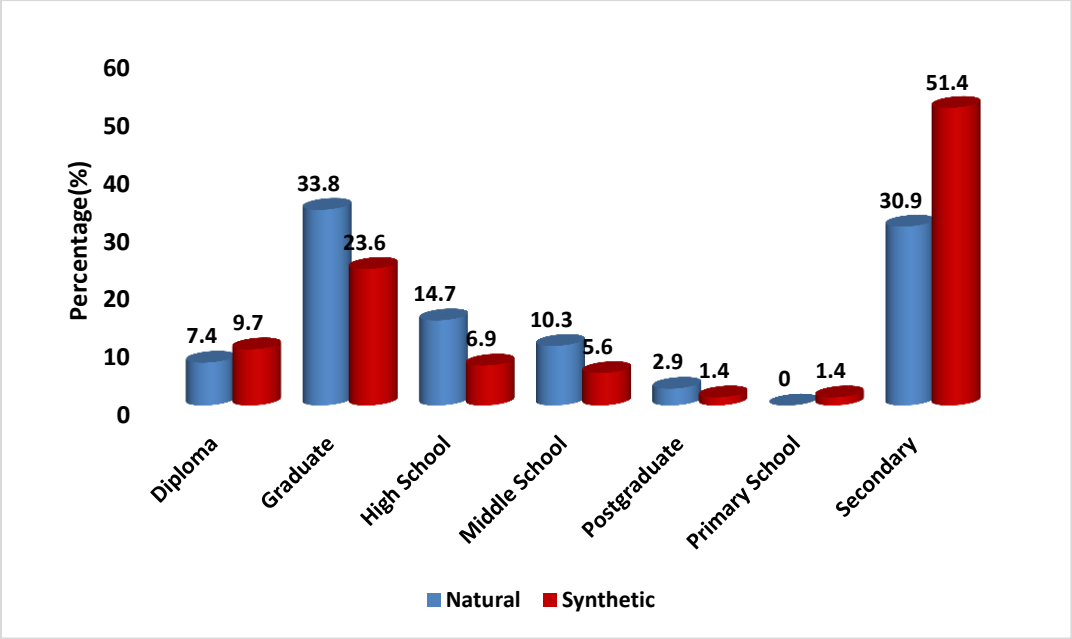


Majority of subjects were married

Table 4: Distribution and association of education with the type of substance used

Education	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
Diploma	5	7.4	7	9.7	12	8.6	9.35	0.154
Graduate	23	33.8	17	23.6	40	28.6		
High school	10	14.7	5	6.9	15	10.7		
Middle school	7	10.3	4	5.6	11	7.9		
Postgraduate	2	2.9	1	1.4	3	2.1		
Primary school	0	0.0	1	1.4	1	0.7		
Secondary	21	30.9	37	51.4	58	41.4		
Total	68	100	72	100	140	100		

Figure 4: Bar graph showing distribution of education with the type of substance used

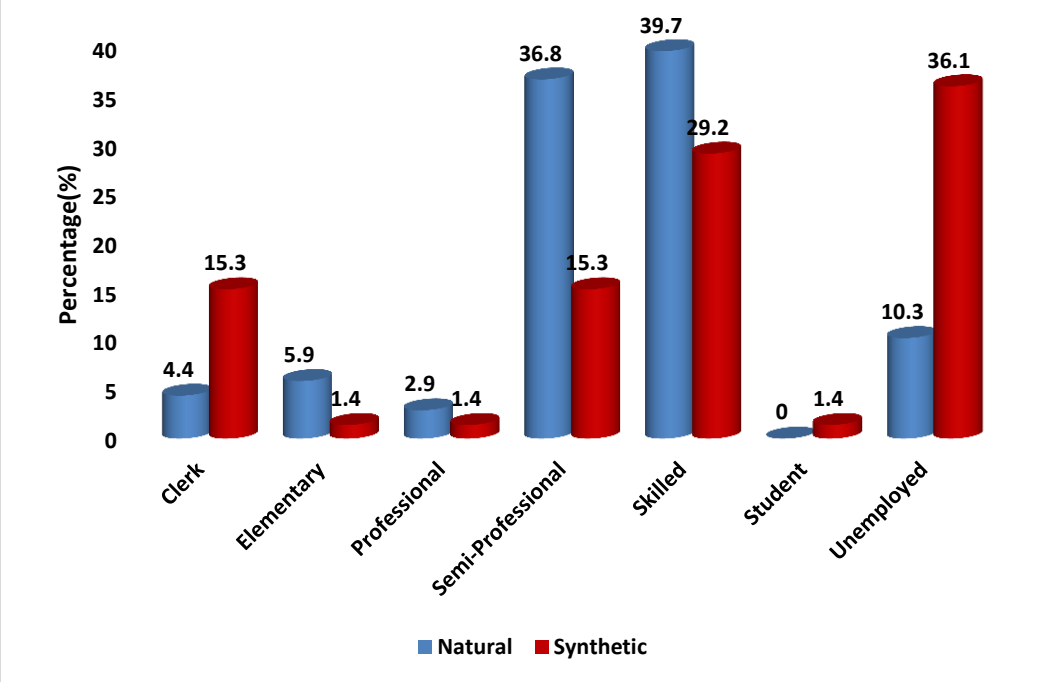


All subjects were literate, the majority attained secondary school or higher education

Table 5: Distribution and association of occupation with the type of substance used

Occupation	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
Clerk	3	4.4	11	15.3	14	10	24.74	**<0.001**
Elementary	4	5.9	1	1.4	5	3.6		
Professional	2	2.9	1	1.4	3	2.1		
Semi-professional	25	36.8	11	15.3	36	25.7		
Skilled	27	39.7	21	29.2	48	34.3		
Student	0	0.0	1	1.4	1	0.7		
Unemployed	7	10.3	26	36.1	33	23.6		
Total	68	100	72	100	140	100		

Figure 5: Bar graph showing distribution of occupation with the type of substance used

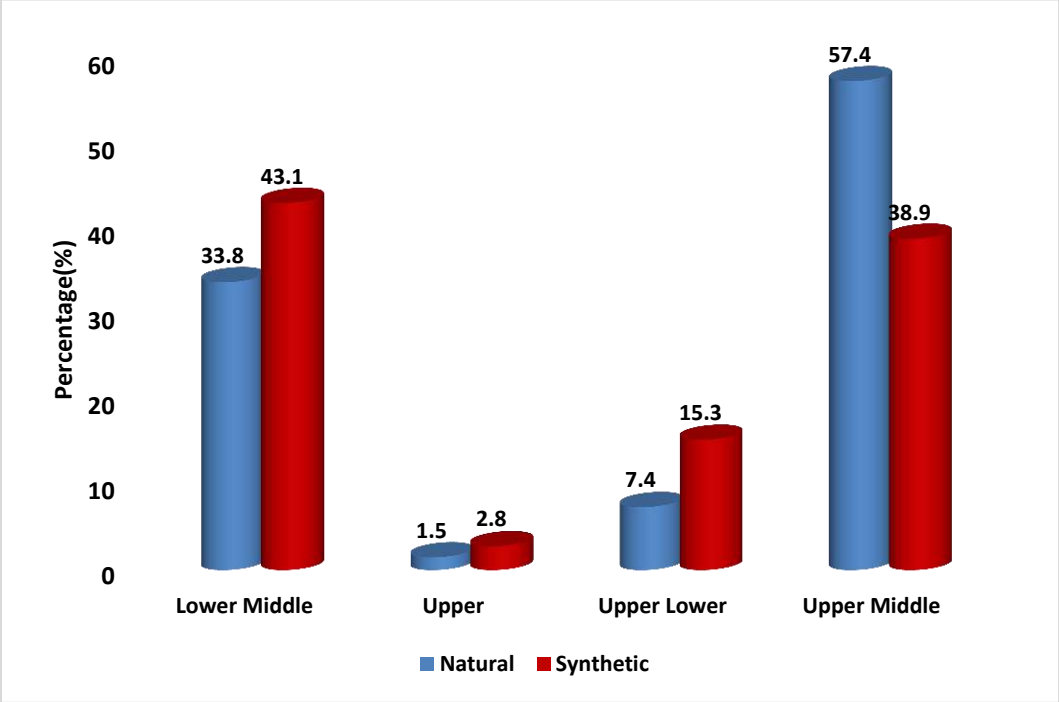


Maximum number of subjects were employed, most of them did skilled and semi-professional jobs, and used natural opioids. Unemployed subjects mainly used synthetic opioids

Table 6: Distribution and association of socioeconomic status with the type of substance used

Socioeconomic status	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
Lower middle	23	33.8	31	43.1	54	38.6	5.46	0.141
Upper	1	1.5	2	2.8	3	2.1		
Upper lower	5	7.4	11	15.3	16	11.4		
Upper middle	39	57.4	28	38.9	67	47.9		
Total	68	100	72	100	140	100		

Figure 6: Bar graph showing distribution of socioeconomic status with the type of substance used

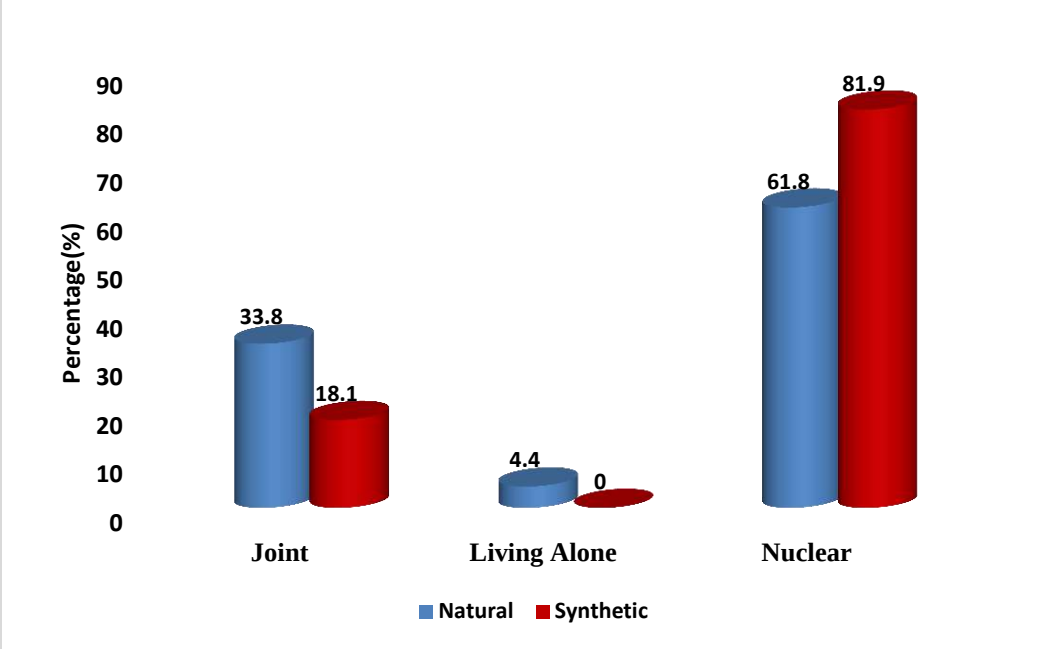


Most of the subjects belonged to the upper middle class

Table 7: Distribution and association of family type with the type of substance used

Family	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
Joint	23	33.8	13	18.1	36	25.7	8.53	**0.014**
Living alone	3	4.4	0	0.0	3	2.1		
Nuclear	42	61.8	59	81.9	101	72.1		
Total	68	100	72	100	140	100		

Figure 7: Bar graph showing distribution of family type with the type of substance used

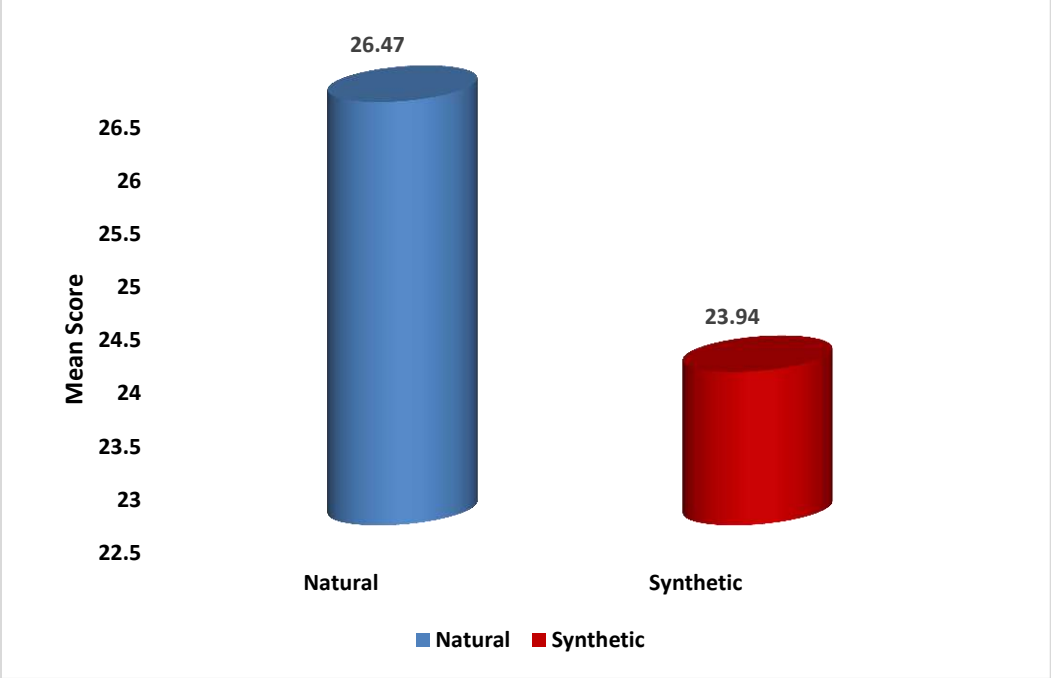


Most of them belonged to nuclear families, and used synthetic opioids predominantly

Table 8: Mean age of onset of opioid dependence

	Substance		t-test	p-value	Cohen's d
	Natural	Synthetic			
	Mean ± SD	Mean ± SD			
Age of onset (in years)	26.47 ± 8.16	23.94 ± 6.6	2.008	**0.047**	0.34

Figure 8: Bar graph showing mean age of onset of opioid dependence

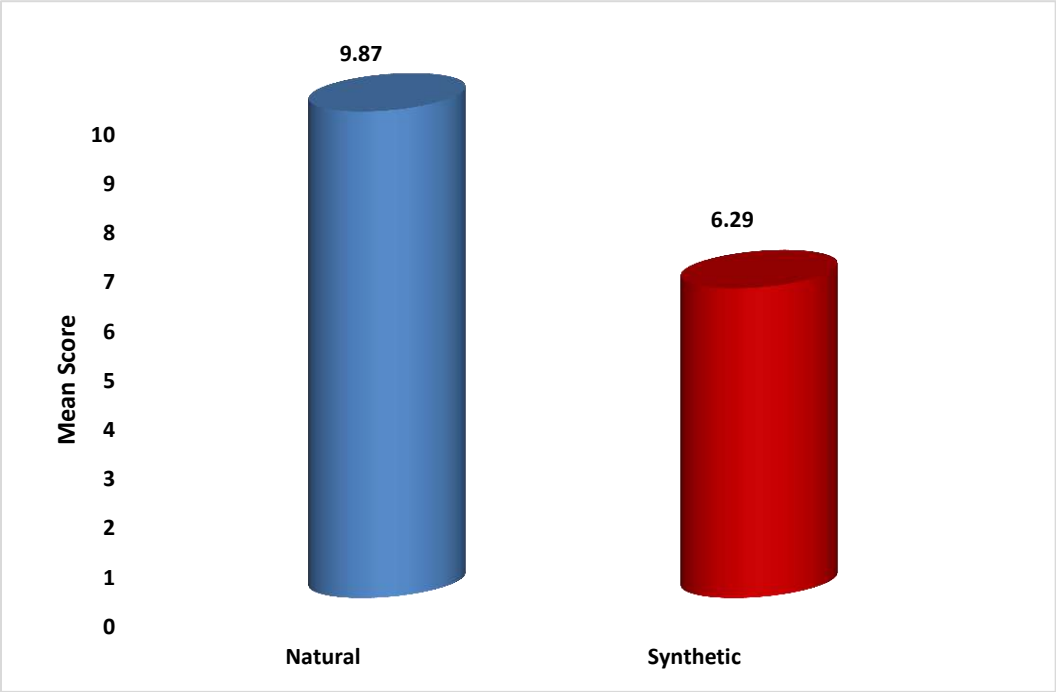


Synthetic opioid users began using the substance at an early age whereas natural opioid users started it at a later age

Table 9: Mean duration of opioid dependence

	Substance		Total	t-test	p-value	Cohen's d
	Natural	Synthetic				
	Mean ± SD	Mean ± SD	Mean ± SD			
Duration (in years)	9.87 ± 6.11	6.29 ± 3.52	8.03 ± 5.25	4.20	**<0.01**	0.71

Figure 9: Bar graph showing mean duration of opioid dependence

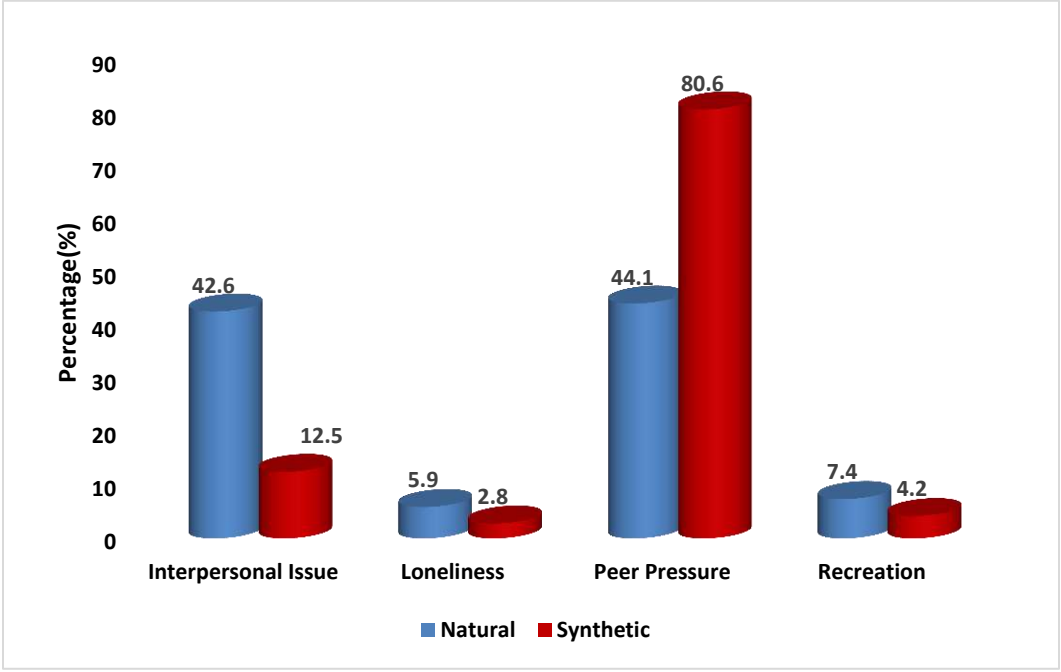


Natural opioids were used for longer duration as compared to synthetic opioids

Table 10: Distribution and association of precipitating factor with the type of substance used

Precipitating factor	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
Interpersonal Issues	29	42.6	9	12.5	38	27.1	20.505	**<0.001**
Loneliness	4	5.9	2	2.8	6	4.3		
Peer Pressure	30	44.1	58	80.6	88	62.9		
Recreation	5	7.4	3	4.2	8	5.7		
Total	68	100	72	100	140	100		

Figure 10: Bar graph showing the distribution of precipitating factor with the type of substance used

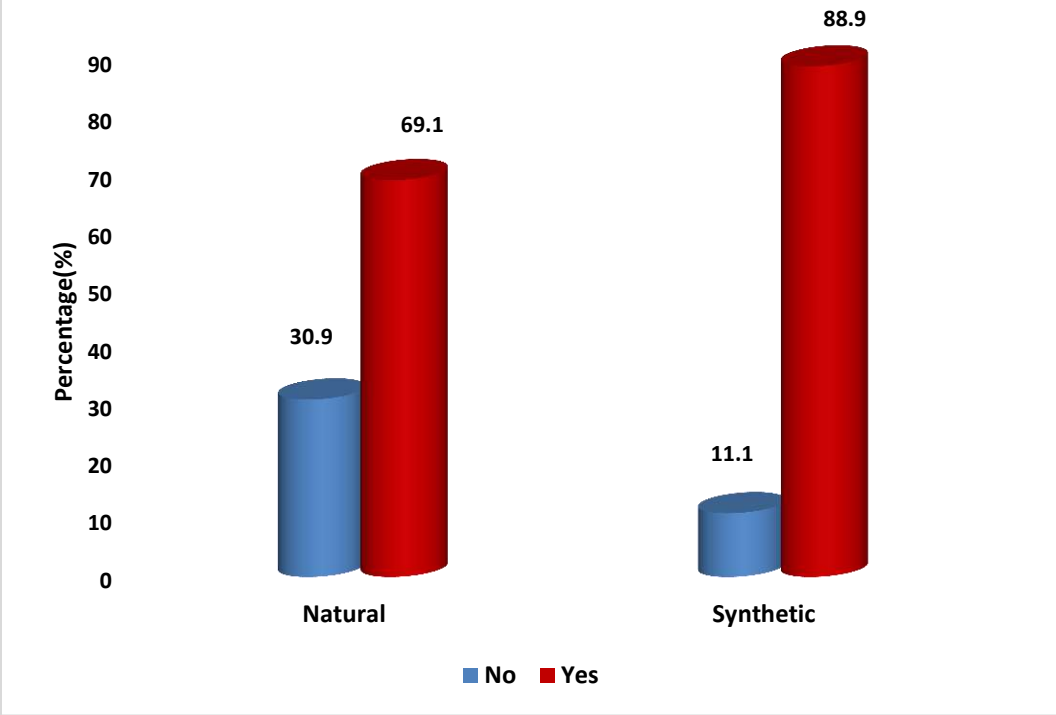


Peer pressure was the most common precipitating factor, especially among synthetic opioid users, and among natural opioid users interpersonal issues also led to the use of substance

Table 11: Distribution and association of comorbid nicotine use with the type of substance used

Comorbid Nicotine	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
No	21	30.9	8	11.1	29	20.7	8.324	**0.004**
Yes	47	69.1	64	88.9	111	79.3		
Total	68	100	72	100	140	100		

Figure 11: Bar graph showing distribution of comorbid nicotine use with the type of substance used

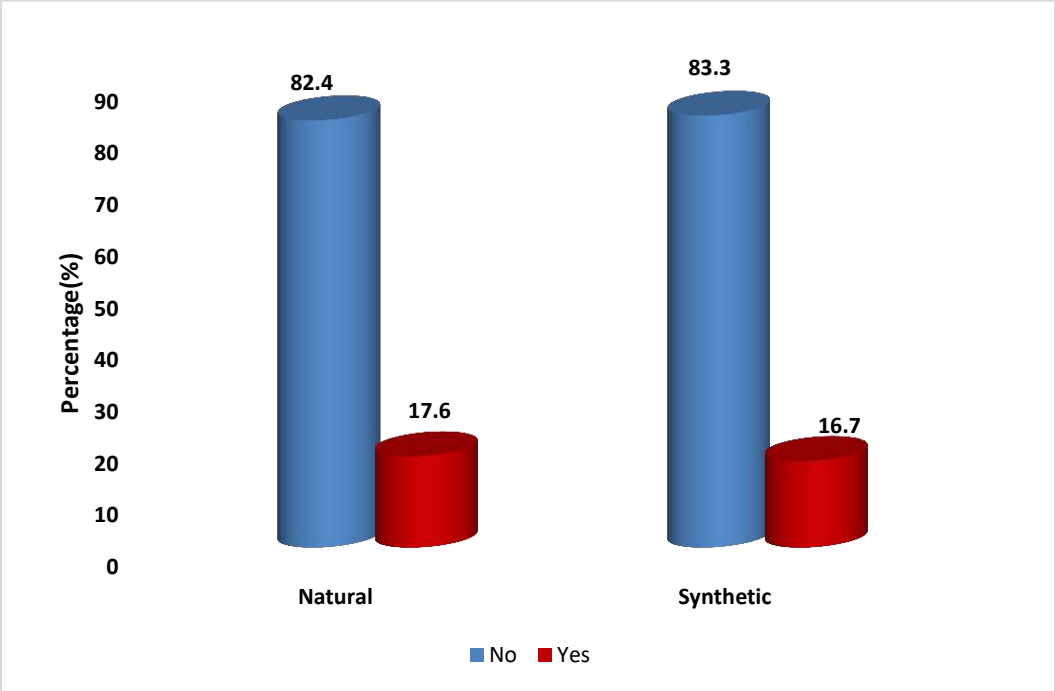


Comorbid nicotine use was prevalent among the majority of opioid users, predominantly among the synthetic opioid users

Table 12: Distribution and association of family history of opioid dependence with the type of substance used

FHO Opioid Dependence	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
No	56	82.4	60	83.3	116	82.9	0.024	0.878
Yes	12	17.6	12	16.7	24	17.1		
Total	68	100	72	100	140	100		

Figure 12: Bar graph showing the presence of family history of opioid dependence with the type of substance used

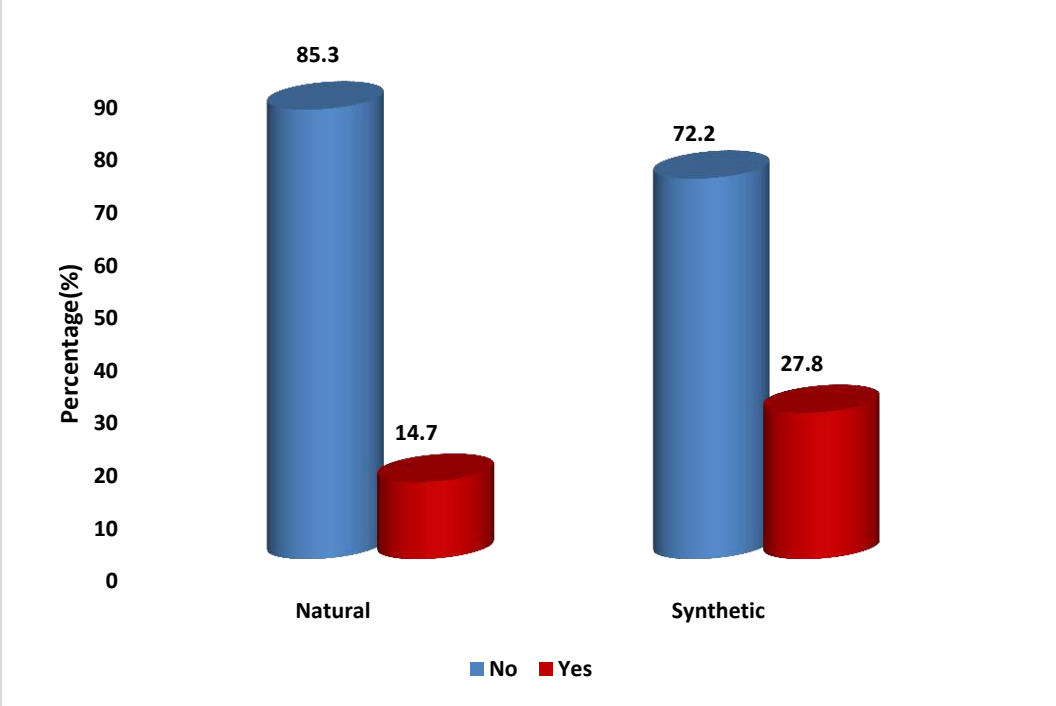


Majority had no family history of opioid dependence

Table 13: Distribution and association of family history of mental illness with the type of substance used

Mental Illness	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
No	58	85.3	52	72.2	110	78.6	3.54	0.60
Yes	10	14.7	20	27.8	30	21.4		
Total	68	100	72	100	140	100		

Figure 13: Bar graph showing the presence of family history of mental illness with the type of substance used

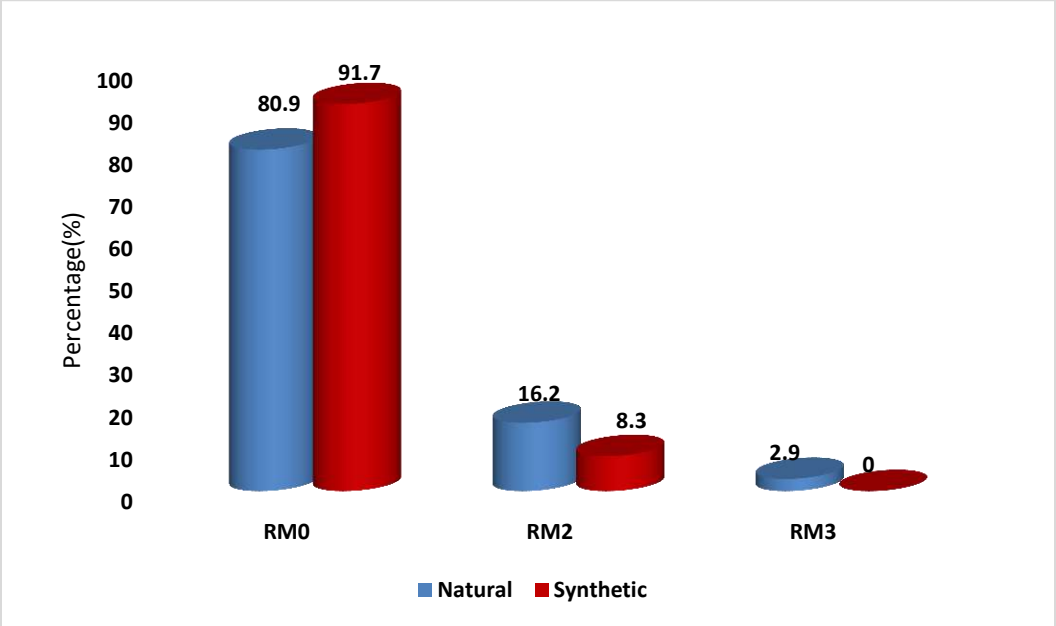


Majority had no family history of mental illness

Table 14: Distribution and association of remote memory with the type of substance used

Remote Memory	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	55	80.9	66	91.7	121	86.4	4.36	0.11
2	11	16.2	6	8.3	17	12.1		
3	2	2.9	0	0.0	2	1.4		
Total	68	100	72	100	140	100		

Figure 14: Bar graph showing scores of Remote Memory

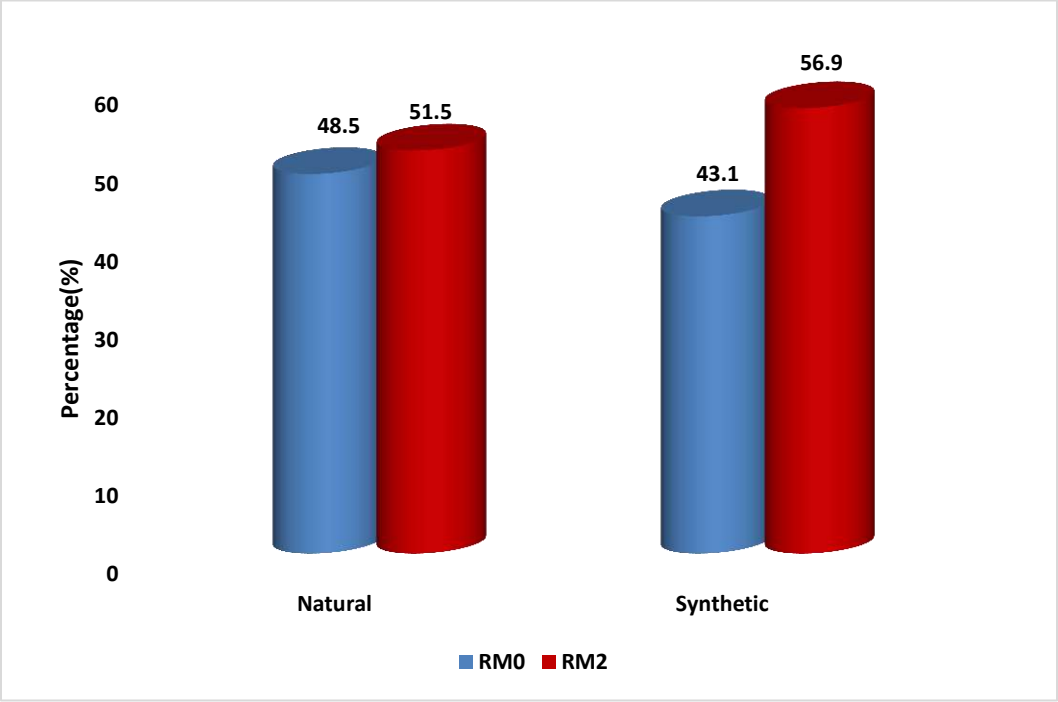


Remote memory was relatively intact among subjects

Table 15: Distribution and association of recent memory with the type of substance used

Recent Memory	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	33	48.5	31	43.1	64	45.7	0.42	0.516
2	35	51.5	41	56.9	76	54.3		
Total	68	100	72	100	140	100		

Figure 15: Bar graph showing scores of Recent Memory

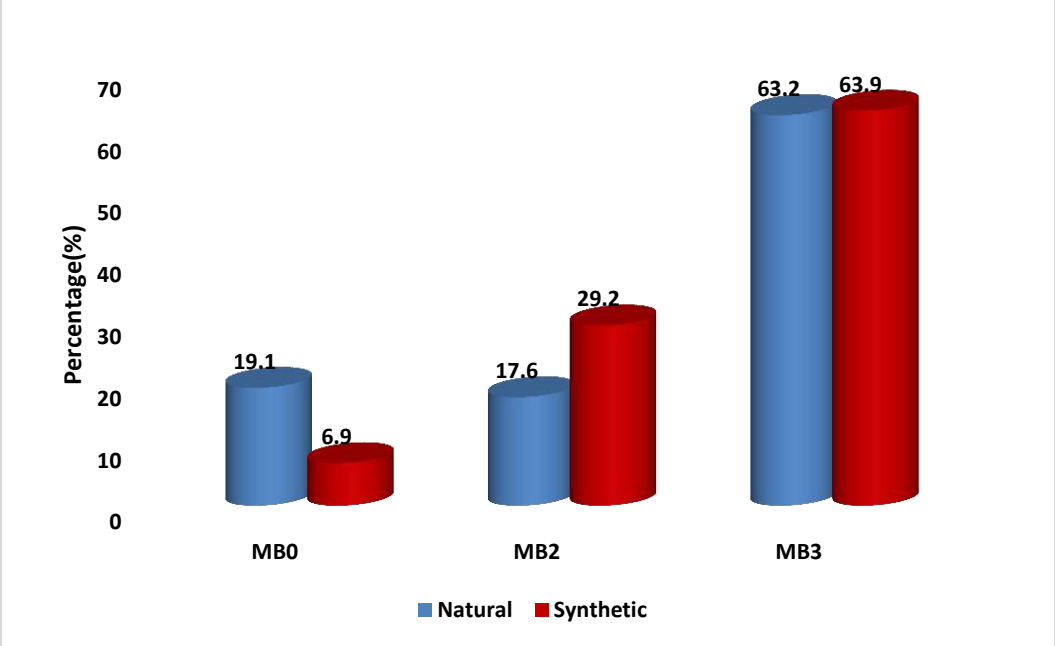


Recent memory was relatively intact among the subjects

Table 16: Distribution and association of mental balance with the type of substance used

Mental Balance	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	13	19.1	5	6.9	18	12.9	6.002	**0.049**
2	12	17.6	21	29.2	33	23.6		
3	43	63.2	46	63.9	89	63.6		
Total	68	100	72	100	140	100		

Figure 16: Bar graph showing scores of Mental Balance

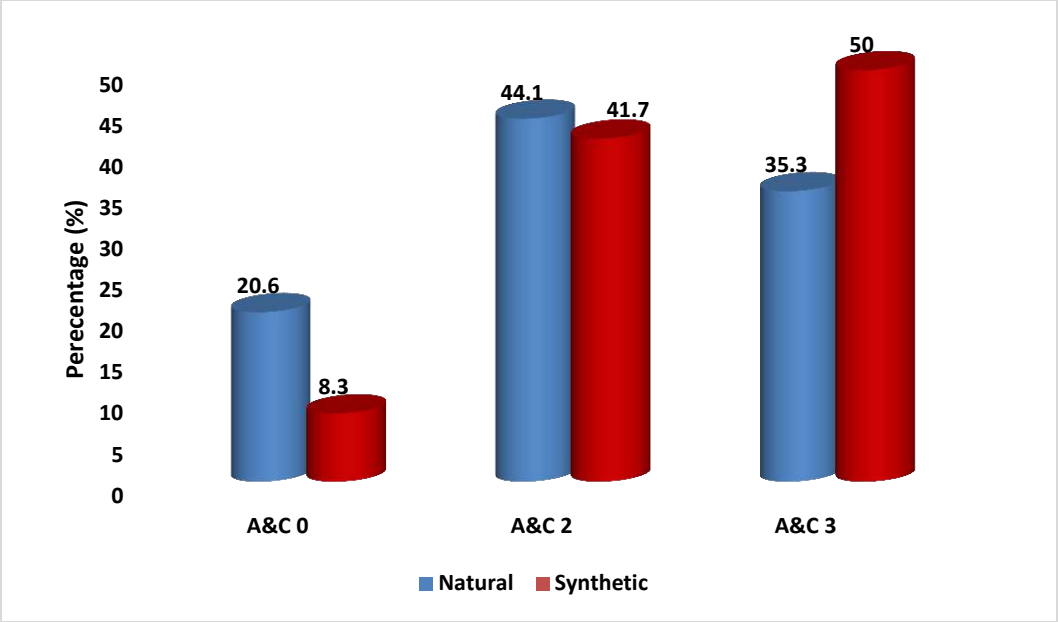


Majority of the subjects scored 3 indicating greater impairment of mental balance, and was seen more in synthetic opioid users.

Table 17: Distribution and association of attention and concentration with the type of substance used

Attention and concentration	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	14	20.6	6	8.3	20	14.3	5.49	0.064
2	30	44.1	30	41.7	60	42.9		
3	24	35.3	36	50	60	42.9		
Total	68	100	72	100	140	100		

Figure 17: Bar graph showing scores of Attention and Concentration

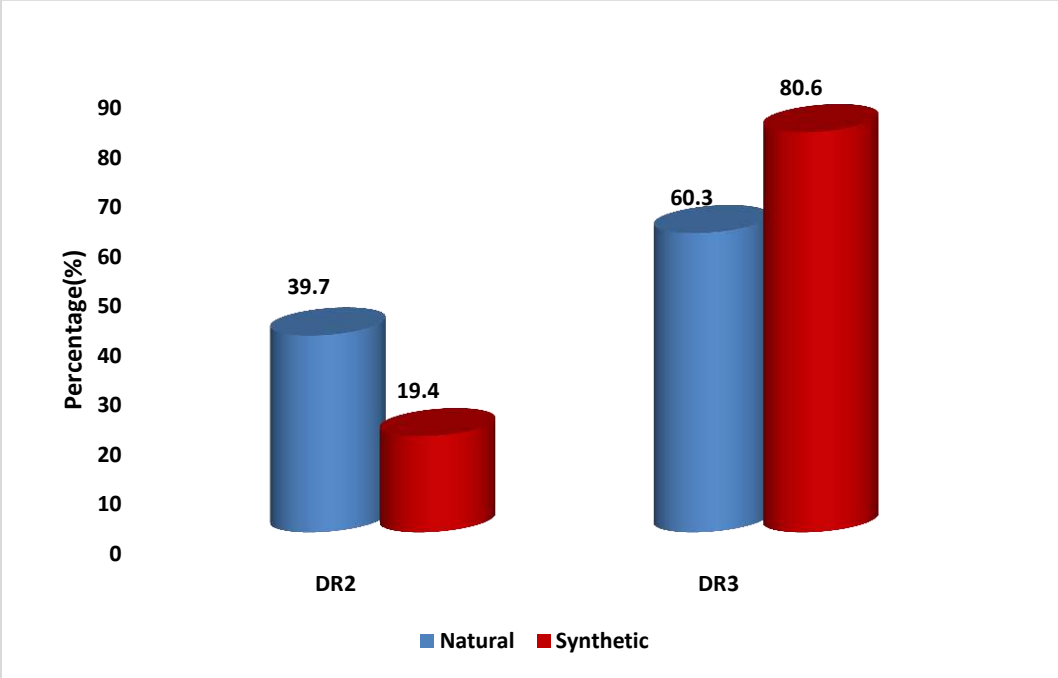


Majority of the subjects scored 2 and 3 which indicated impairment in attention and concentration of the subjects, the difference between the two groups was not significant.

Table 18: Distribution and association of delayed recall with the type of substance used

Delayed recall	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
2	27	39.7	14	19.4	41	29.3	6.93	**0.008**
3	41	60.3	58	80.6	99	70.7		
Total	68	100	72	100	140	100		

Figure 18: Bar graph showing scores of Delayed Recall

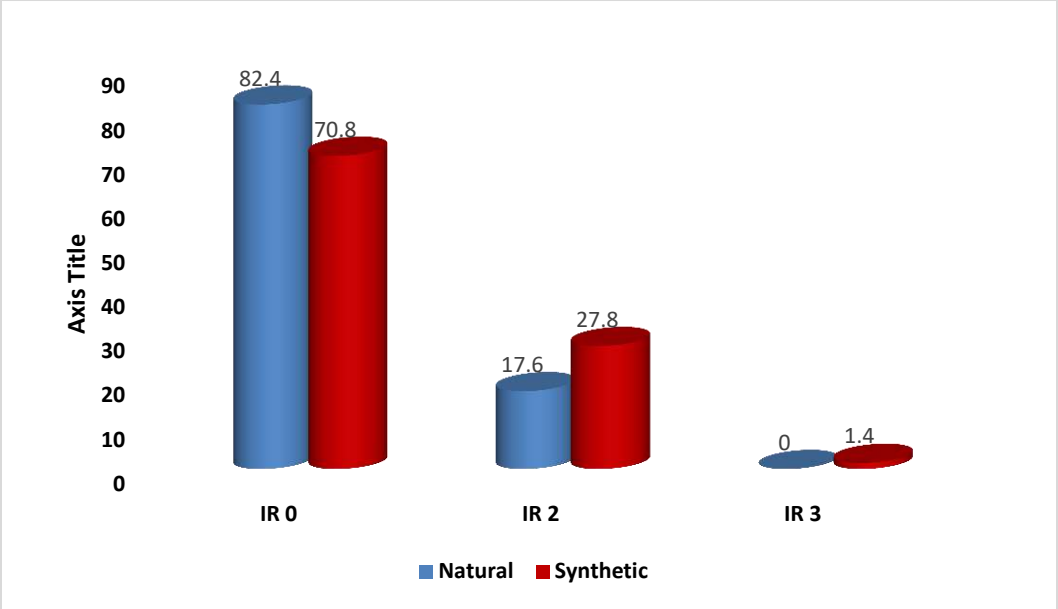


Majority of the subjects scored 2 and 3 which indicated impairment in delayed recall of the subjects, predominantly seen in the synthetic opioid users, the difference between the two groups was significant.

Table 19: Distribution and association of immediate recall with the type of substance used

Immediate recall	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	56	82.4	51	70.8	107	76.4	3.12	0.21
2	12	17.6	20	27.8	32	22.9		
3	0	0.0	1	1.4	1	0.7		
Total	68	100	72	100	140	100		

Figure 19: Bar graph showing scores of Immediate Recall

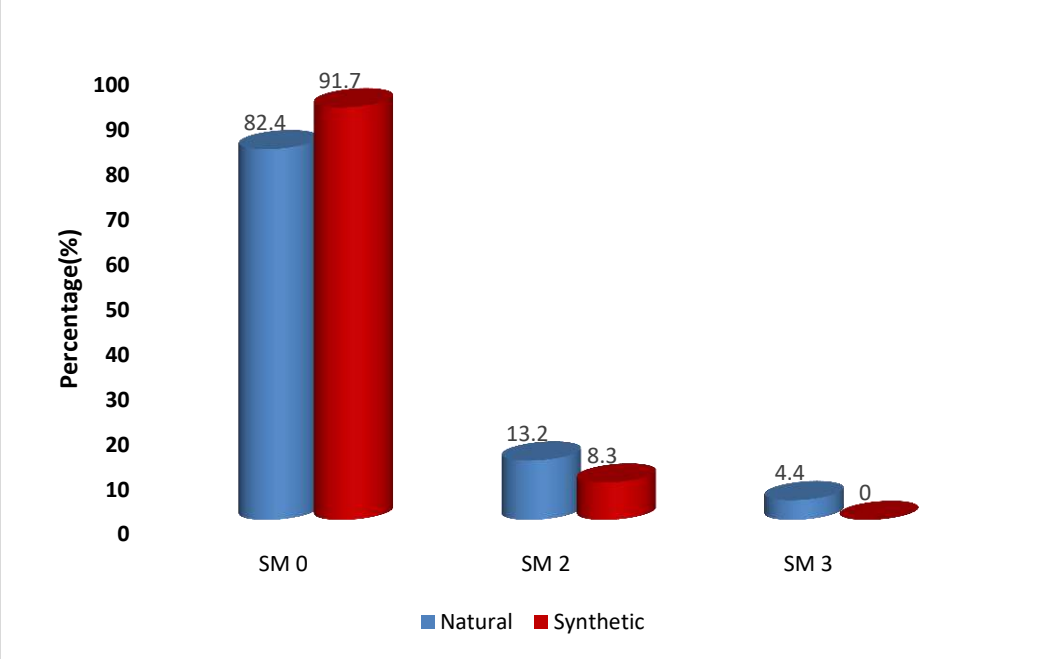


Immediate recall was relatively intact among the subjects

Table 20: Distribution and association of retention for similar pairs with the type of substance used

Retention for similar pairs	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	56	82.4	66	91.7	122	87.1	4.30	0.116
2	9	13.2	6	8.3	15	10.7		
3	3	4.4	0	0.0	3	2.1		
Total	68	100	72	100	140	100		

Figure 20: Bar graph showing scores of Retention of Similar Pairs

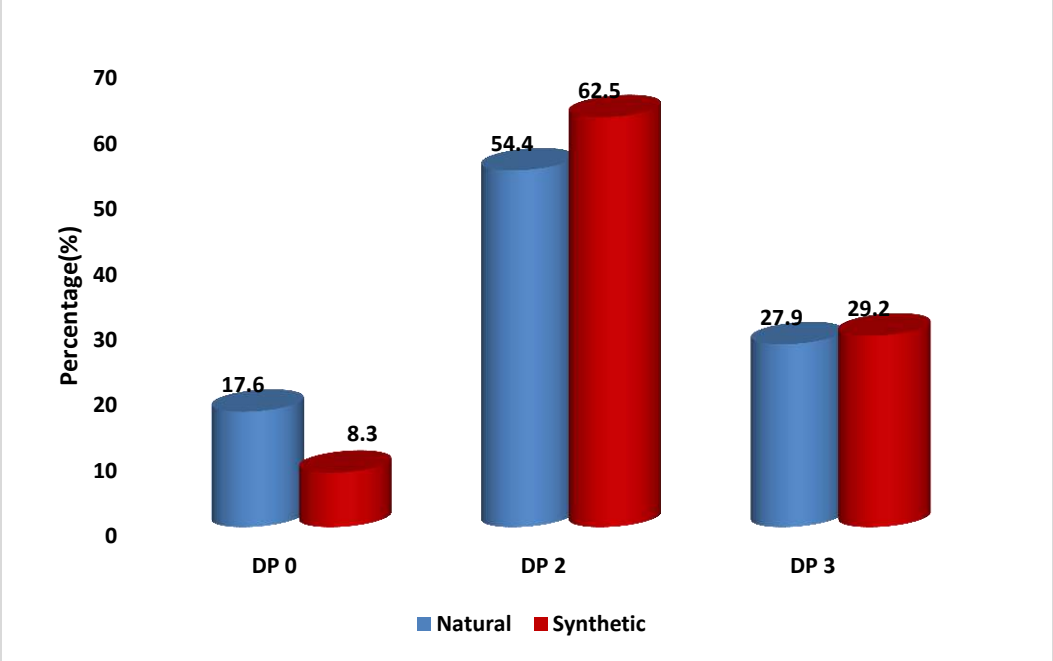


Retention of Similar Pairs was relatively intact among the subjects

Table 21: Distribution and association of retention for dissimilar pairs with the type of substance used

Retention for dissimilar pairs	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	12	17.6	6	8.3	18	12.9	2.76	0.25
2	37	54.4	45	62.5	82	58.6		
3	19	27.9	21	29.2	40	28.6		
Total	68	100	72	100	140	100		

Figure 21: Bar graph showing scores of Retention of Dissimilar Pairs

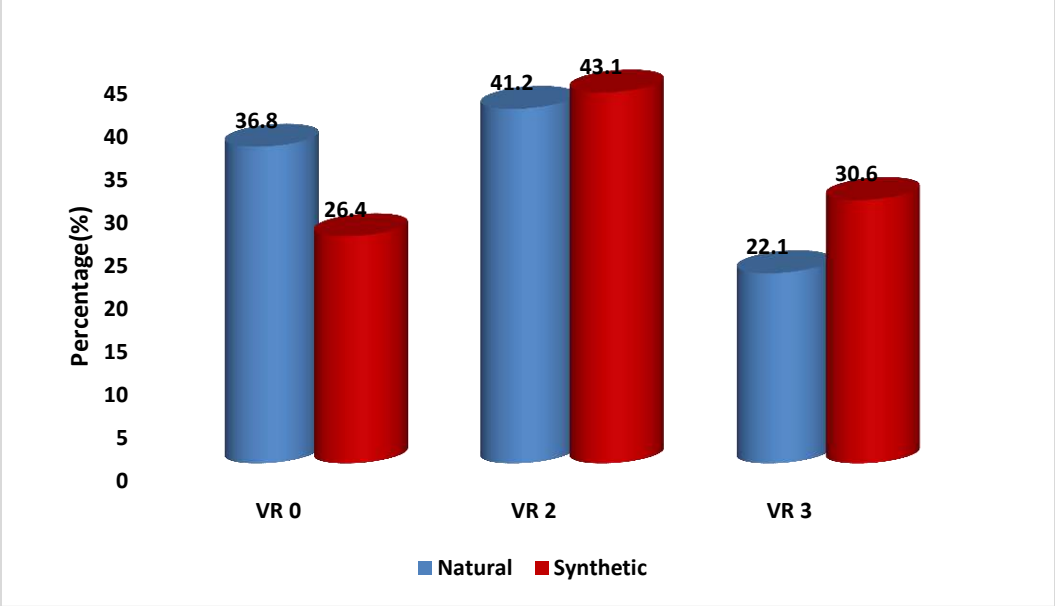


Retention of dissimilar pairs was impaired among the subjects, the difference between the two groups was not significant

Table 22: Distribution and association of visual retention with the type of substance used

Visual Retention	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	25	36.8	19	26.4	44	31.4	2.18	0.366
2	28	41.2	31	43.1	59	42.1		
3	15	22.1	22	30.6	37	26.4		
Total	68	100	72	100	140	100		

Figure 22: Bar graph showing scores of Visual Retention

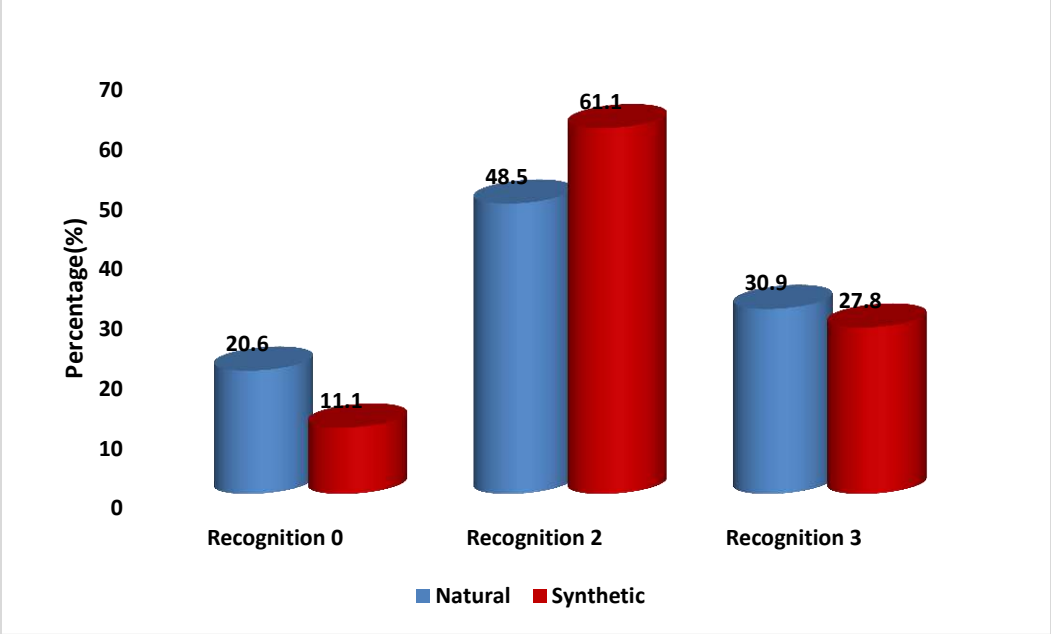


Visual Retention was impaired among the subjects, the difference between the two groups was not significant

Table 23: Distribution and association of recognition with the type of substance used

Recognition	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	14	20.6	8	11.1	22	15.7	3.12	0.21
2	33	48.5	44	61.1	77	55.0		
3	21	30.9	20	27.8	41	29.3		
Total	68	100	72	100	140	100		

Figure 23: Bar graph showing scores of Recognition

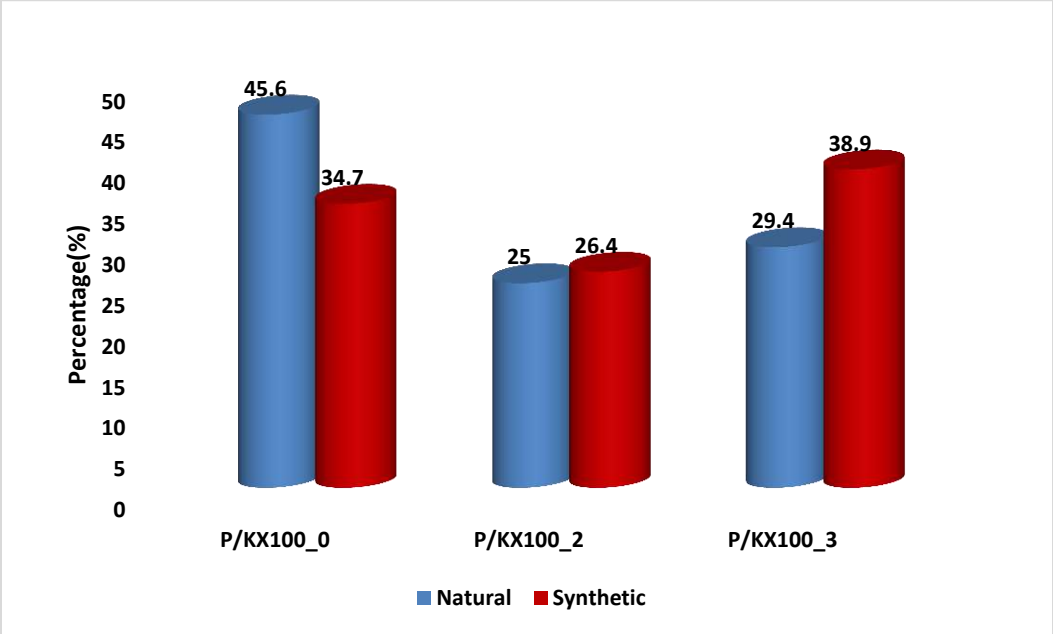


Recognition was impaired among the subjects, more in the synthetic opioid users, the difference between the two groups was not significant

Table 24: Distribution and association of P/KX100 with the type of substance used

P/KX100	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	31	45.6	25	34.7	56	40.0	1.97	0.37
2	17	25	19	26.4	36	25.7		
3	20	29.4	28	38.9	48	34.3		
Total	68	100	72	100	140	100		

Figure 24: Bar graph showing scores of P/KX100

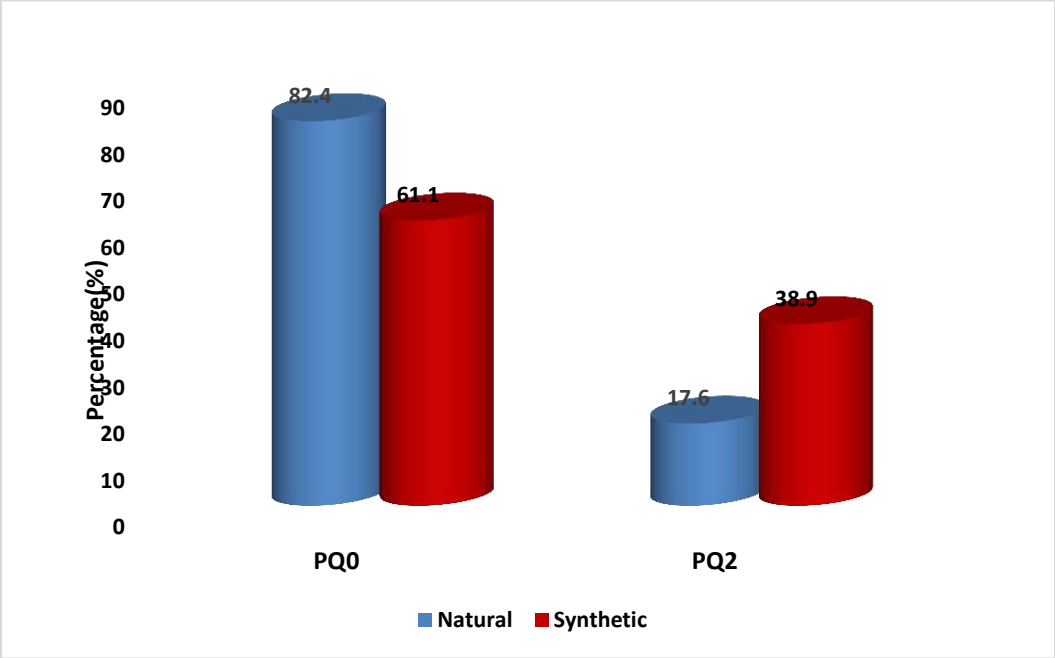


Shows P/KX100 was impaired among the subjects, more among the synthetic opioid users, the difference between the two groups was not significant

Table 25: Distribution and association of PQ with the type of substance used

Performance Quotient	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	56	82.4	44	61.1	100	71.4	7.732	**0.005**
2	12	17.6	28	38.9	40	28.6		
Total	68	100	72	100	140	100		

Figure 25: Bar graph showing scores of Performance Quotient (PQ)

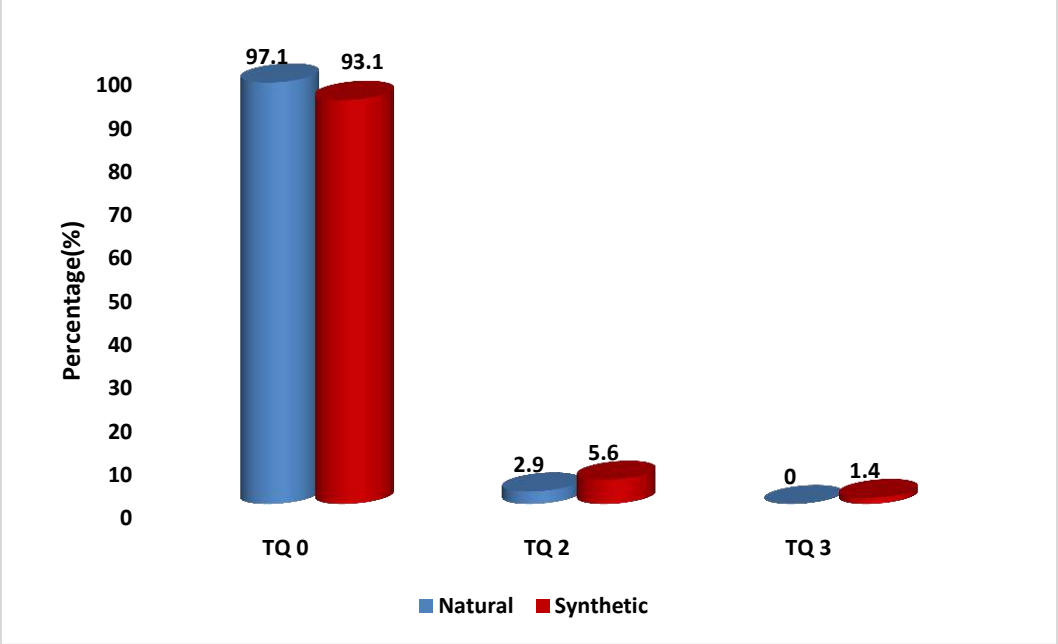


PQ was impaired among synthetic opioid users, the difference between the two groups was significant

Table 26: Distribution and association of TQ information with the type of substance used

TQ Information	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	66	97.1	67	93.1	133	95	1.56	0.458
2	2	2.9	4	5.6	6	4.3		
3	0	0	1	1.4	1	0.7		
Total	68	100	72	100	140	100		

Figure 26: Bar graph showing scores of TQ information

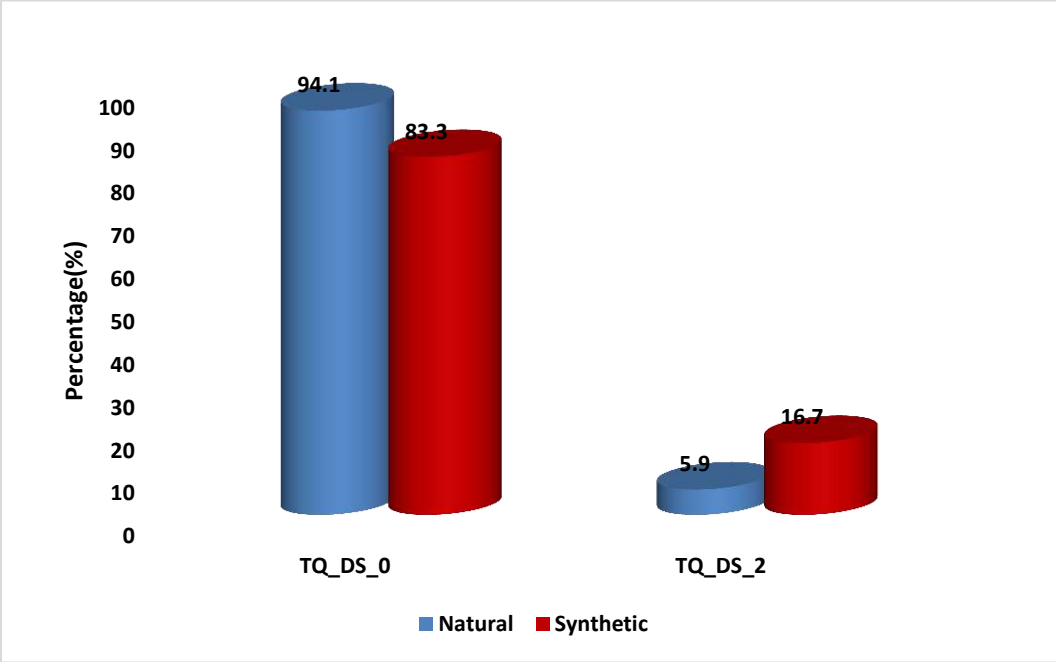


TQ information was relatively intact among the subjects

Table 27: Distribution and association of TQ digit span with the type of substance used

TQ Digit Span	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	64	94.1	60	83.3	124	88.6	4.018	**0.045**
2	4	5.9	12	16.7	16	11.4		
Total	68	100	72	100	140	100		

Figure 27: Bar graph showing scores of TQ Digit Span

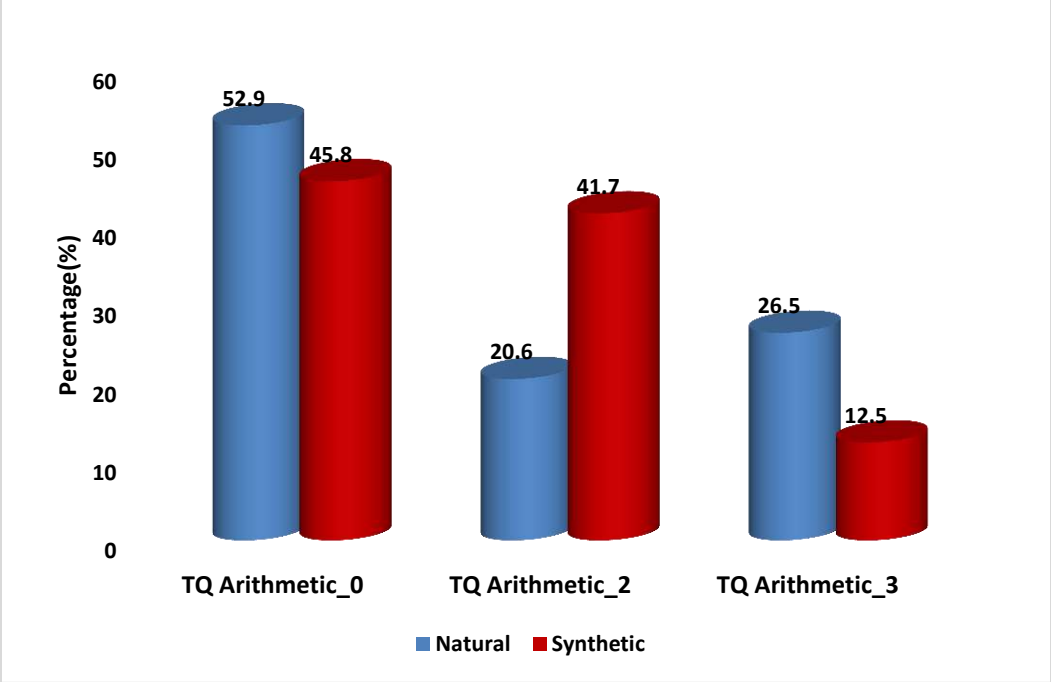


Individuals who used synthetic opioids exhibited impairment in TQ Digit span as compared to those who used natural opioids, the difference between the two groups was significant.

Table 28: Distribution and association of TQ arithmetic with the type of substance used

TQ Arithmetic	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	36	52.9	33	45.8	69	49.3	8.842	**0.012**
2	14	20.6	30	41.7	44	31.4		
3	18	26.5	9	12.5	27	19.3		
Total	68	100	72	100	140	100		

Figure 28: Bar graph showing scores of TQ Arithmetic

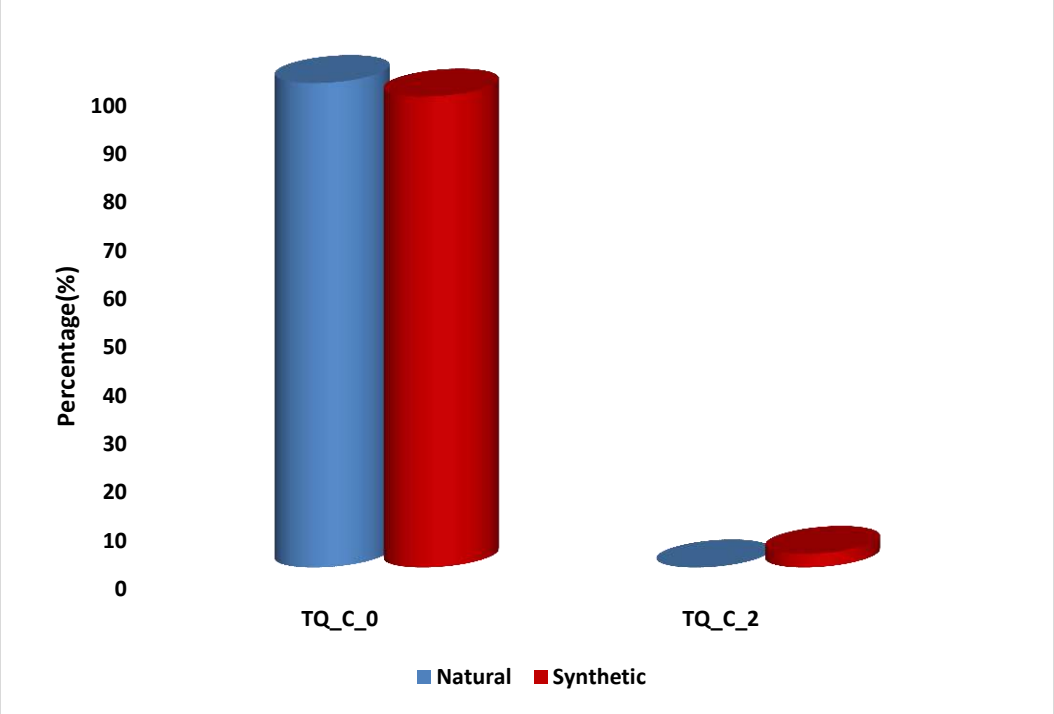


TQ Arithmetic was impaired among the subjects, more so among the synthetic opioid users, the difference between the two groups was significant.

Table 29: Distribution and association of TQ comprehension with the type of substance used

TQ Comprehension	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	68	100	70	97.2	138	98.6	1.91	0.166
2	0	0.0	2	2.8	2	1.4		
Total	68	100	72	100	140	100		

Figure 29: Bar graph showing scores of TQ Comprehension

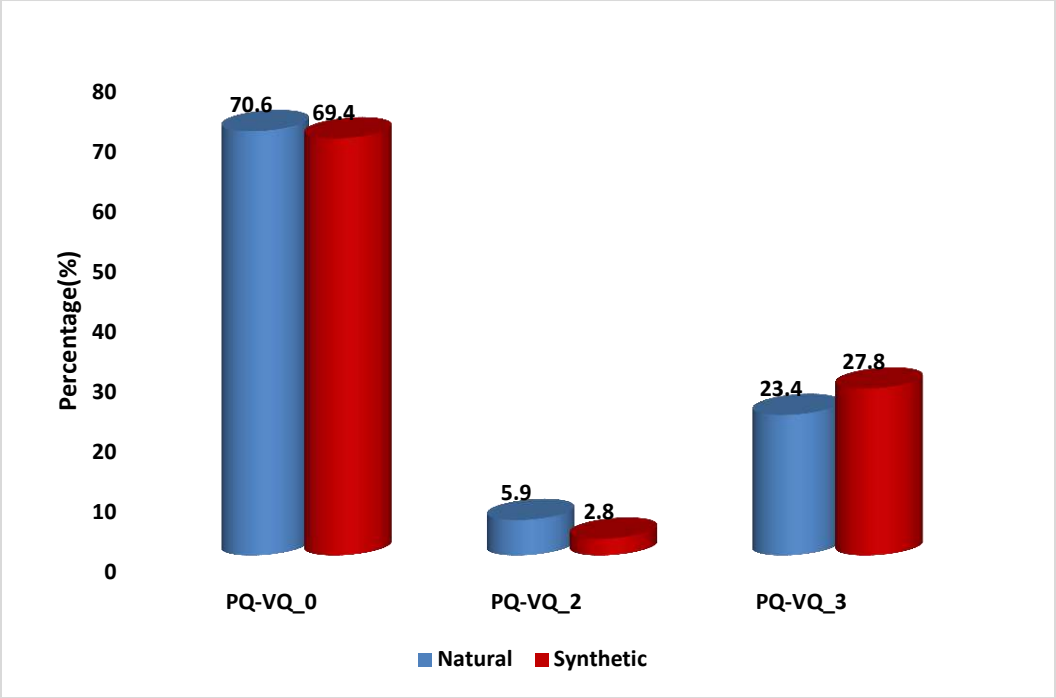


TQ comprehension was relatively intact among the subjects

Table 30: Distribution and association of PQ-VQ with the type of substance used

PQ-VQ	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	48	70.6	50	69.4	98	70	1.038	0.595
2	4	5.9	2	2.8	6	4.3		
3	16	23.4	20	27.8	36	25.7		
Total	68	100	72	100	140	100		

Figure 30: Bar graph showing scores of PQ-VQ

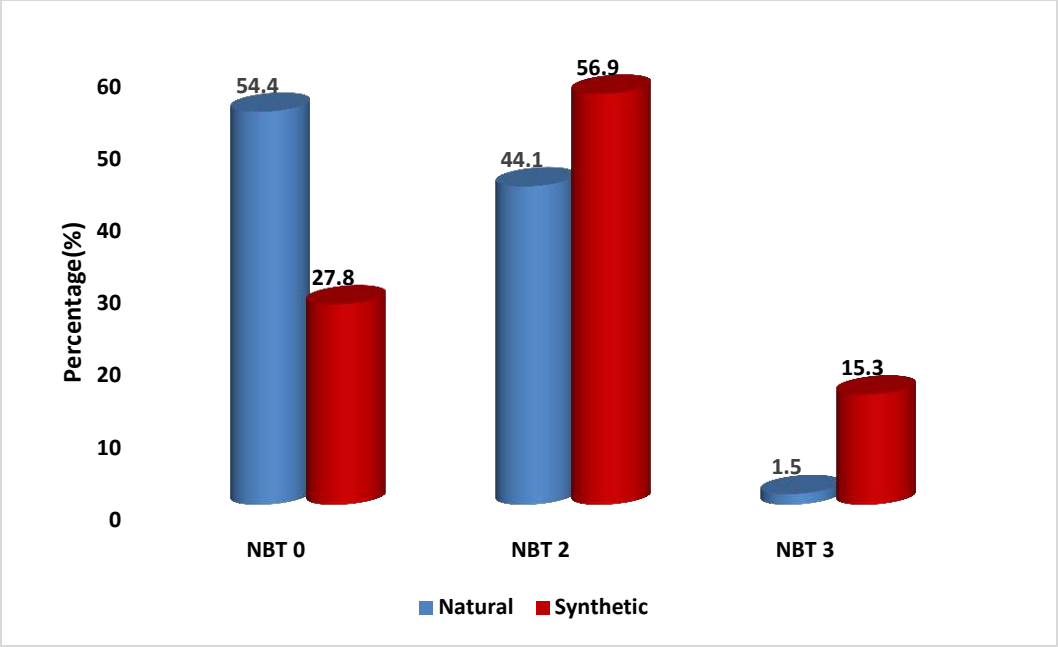


PQ-VQ was impaired among the subjects, more in synthetic opioid users

Table 31: Distribution and association of Nahor Benson Test with the type of substance used

NBT	Substance				Total		Chi-Square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
0	37	54.4	20	27.8	57	40.7	15.00	**0.001**
2	30	44.1	41	56.9	71	50.7		
3	1	1.5	11	15.3	12	8.6		
Total	68	100	72	100	140	100		

Figure 31: Bar graph showing scores of Nahor Benson Test

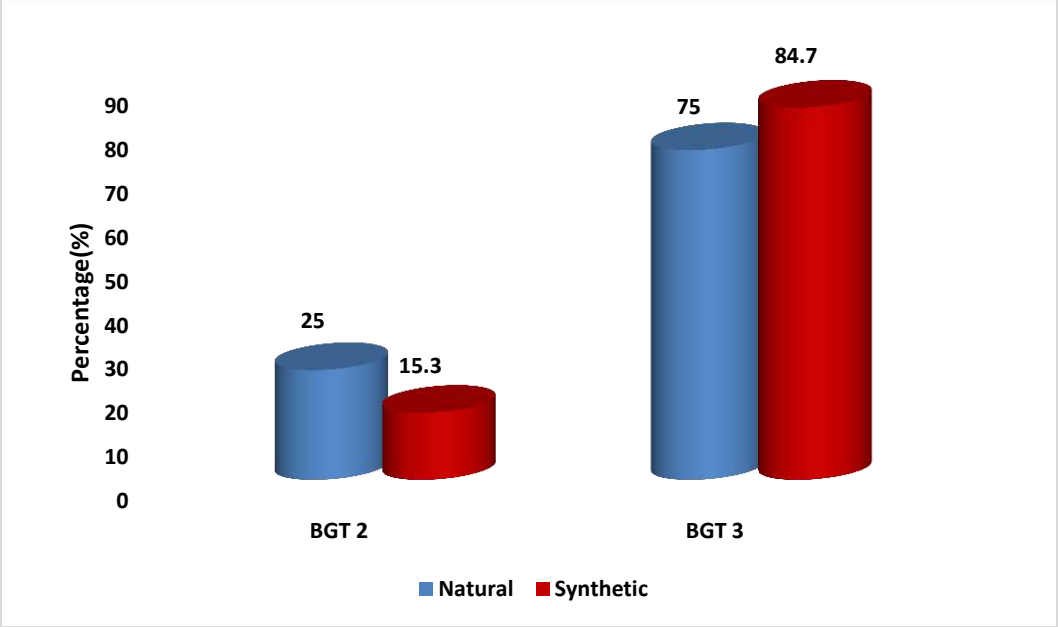


Nahor Benson Test was impaired among the subjects, more among the synthetic opioid users, and the difference between the two groups was significant

Table 32: Distribution and association of bender gestalt test with the type of substance used

Bender Gestalt Test	Substance				Total		Chi-square	p-value
	Natural		Synthetic					
	N	%	N	%	N	%		
2	17	25.0	11	15.3	28	20.0	2.066	0.151
3	51	75	61	84.7	112	80		
Total	68	100	72	100	140	100		

Figure 32: Bar graph showing scores of the Bender Gestalt Test

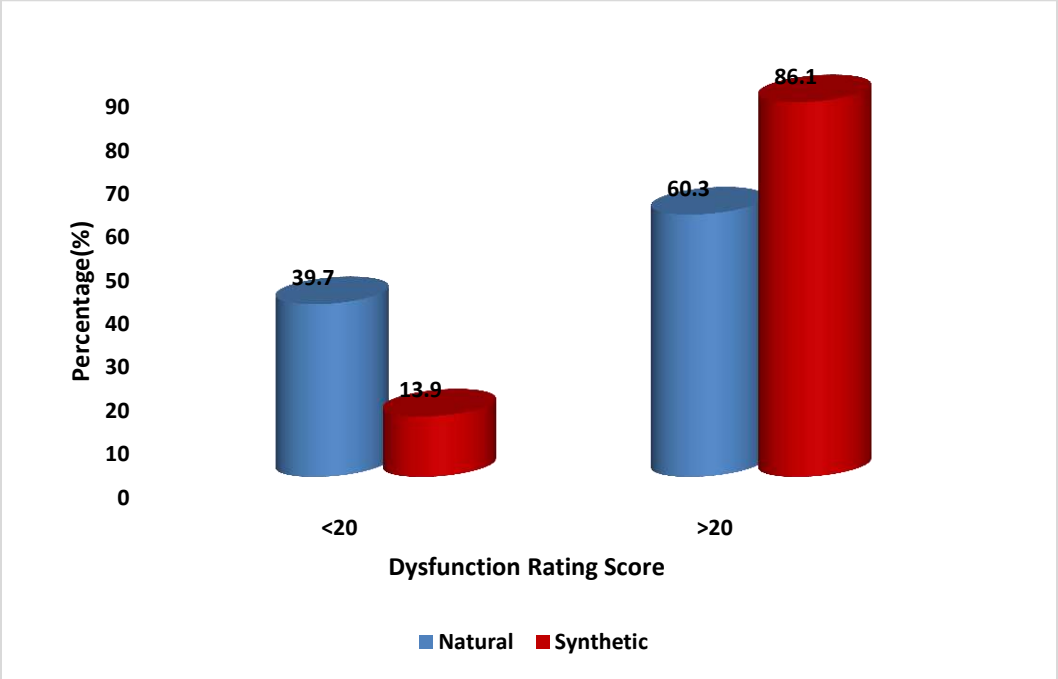


Bender Gestalt Test was impaired among the subjects, more among the synthetic opioid users, the difference between the two groups was not significant

Table 33: Dysfunction rating score among study groups

Dysfunction Rating Score	Substance				Total	
	Natural		Synthetic			
	N	%	N	%	N	%
<20	27	39.7	10	13.9	37	26.4
>20	41	60.3	62	86.1	103	73.6
Total	68	100	72	100	140	100

Figure 33: Bar graph showing Dysfunction Rating Score

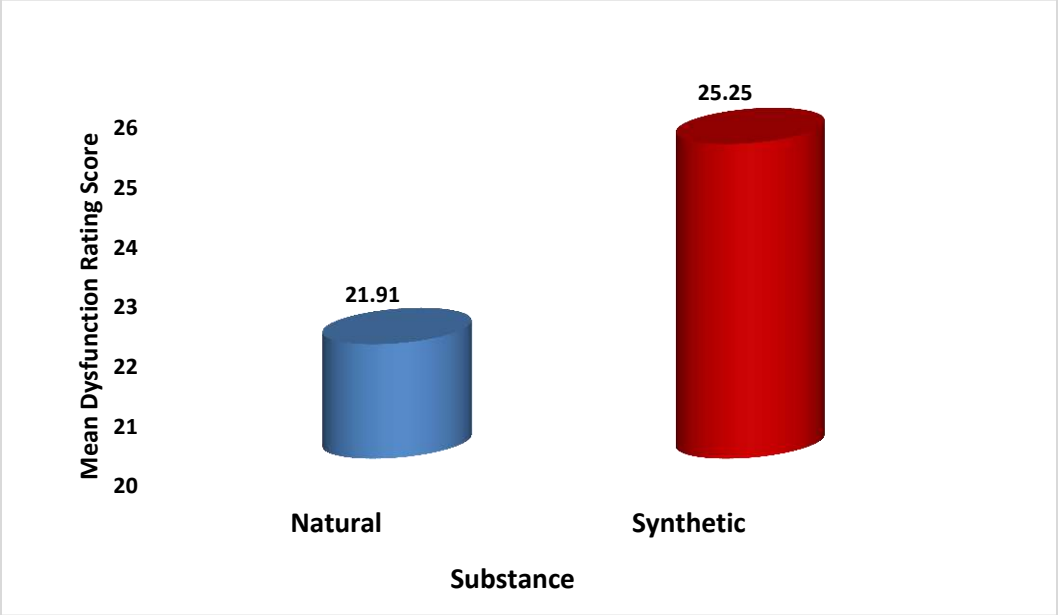


Majority attained a higher dysfunction rating score indicating more cognitive dysfunction among opioid users, particularly synthetic opioid users

Table 34: Mean dysfunction rating score between the study groups

	Substance		t-test	p-value	Cohen's d
	Natural	Synthetic			
	Mean ± SD	Mean ± SD			
Dysfunction Rating Score	21.91 ± 6.54	25.25 ± 6.39	3.054	**0.003**	0.51

Figure 34: Bar graph showing Mean Dysfunction Rating Score

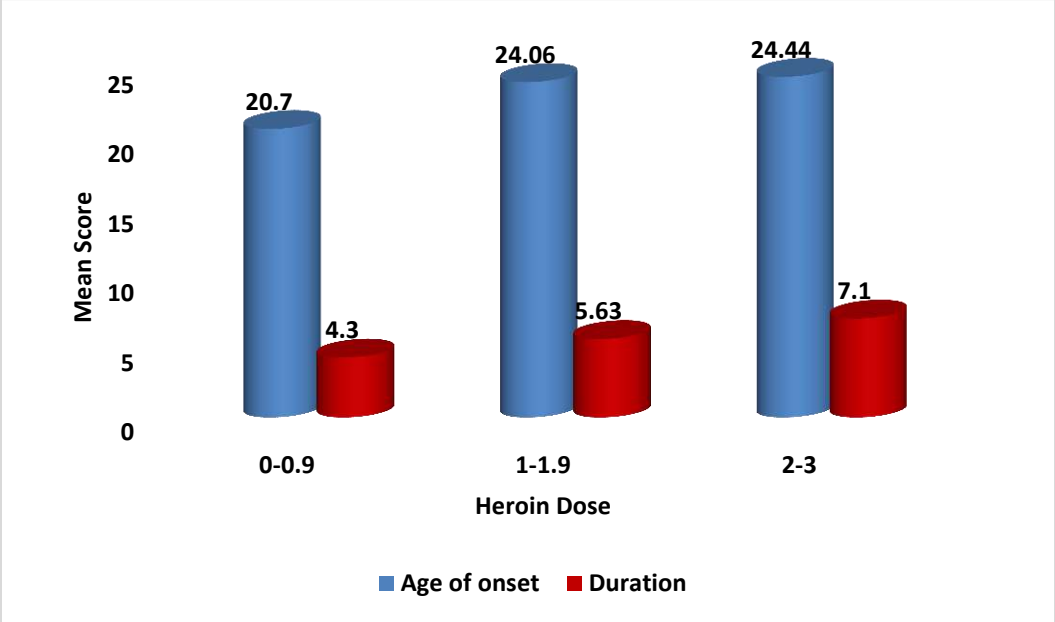


Mean dysfunction rating score was higher in synthetic opioid users, which indicated more cognitive disturbance in them

Table 35: Clinical variables according to heroin dose

Variables	Dose						F	p-value
	0-0.9		1-1.9		2-3.0			
	Mean	SD	Mean	SD	Mean	SD		
Age of onset	20.7	3.02	24.06	6.66	24.44	6.24	1.49	0.23
Duration	4.3	2.54	5.63	3.28	7.10	3.69	3.30	**0.043**

Figure 35: Bar graph showing clinical variables according to heroin dose

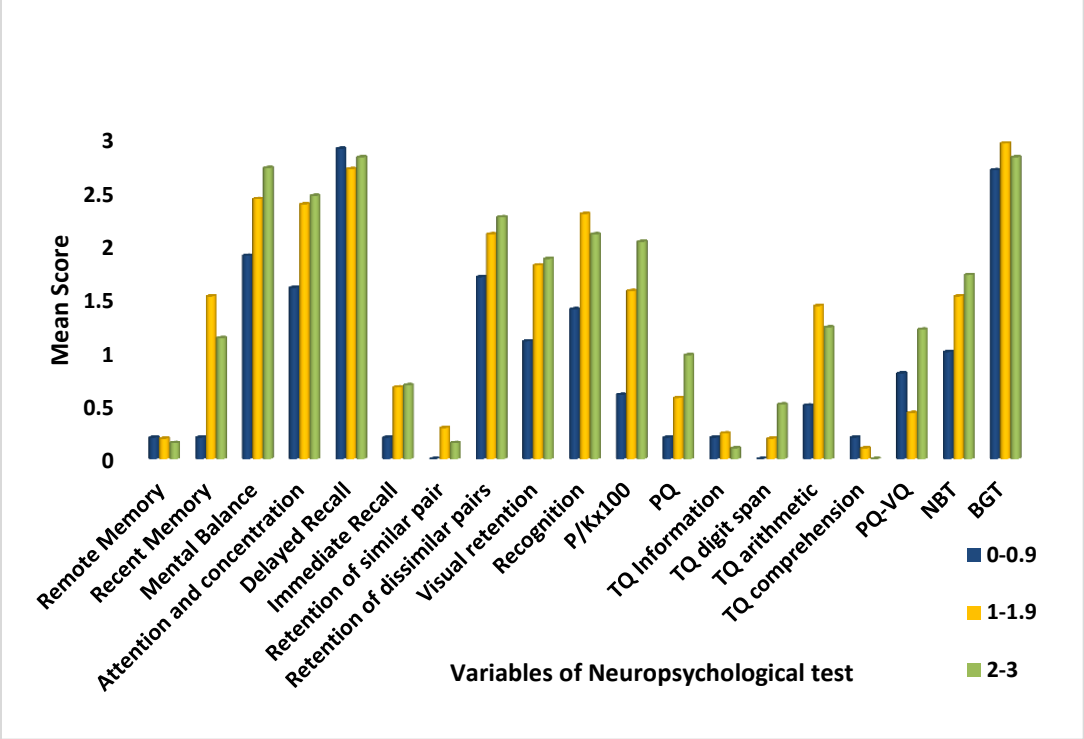


Age of onset increased with higher doses. Users with higher doses had a longer duration of use compared to those who used lower doses.

Table 36: Mean scores of variables of neuropsychological test at different doses of heroin

Variables	Dose(gm)						F	p-value
	0-0.9		1-1.9		2-3			
	Mean	SD	Mean	SD	Mean	SD		
Remote memory	0.20	0.63	0.19	0.60	0.15	0.52	0.04	0.95
Recent memory	0.20	0.63	1.52	0.87	1.13	1.00	6.96	**0.002**
Mental balance	1.9	1.10	2.43	1.07	2.72	0.45	4.42	**0.016**
Attention and concentration	1.6	1.17	2.38	0.92	2.46	0.64	4.49	**0.015**
Delayed recall	2.9	0.31	2.71	0.46	2.82	0.38	0.83	0.44
Immediate recall	0.20	0.63	0.67	0.96	0.69	1.00	1.11	0.33
Retention of similar pair	0.00	0.00	0.29	0.71	0.15	0.54	0.91	0.40
Retention of dissimilar pairs	1.70	0.94	2.10	0.83	2.26	0.71	2.02	0.14
Visual retention	1.10	1.19	1.81	1.25	1.87	1.05	1.88	0.15
Recognition	1.40	1.26	2.29	0.71	2.10	0.75	3.97	**0.022**
P/Kx100	0.60	1.26	1.57	1.20	2.03	1.26	5.31	**0.007**
PQ	0.20	0.63	0.57	0.92	0.97	1.01	3.17	**0.048**
TQ information	0.20	0.63	0.24	0.76	0.10	0.44	0.39	0.67
TQ digit span	0.00	0.00	0.19	0.60	0.51	0.88	2.52	0.08
TQ arithmetic	0.50	1.08	1.43	1.20	1.23	1.13	2.27	0.11
TQ Comprehension	0.20	0.63	0.10	0.43	0.00	0.00	1.63	0.20
PQ-VQ	0.80	1.31	0.43	1.07	1.21	1.47	2.31	0.10
NBT	1.00	1.05	1.52	1.16	1.72	0.94	1.94	0.15
BGT	2.70	0.48	2.95	0.21	2.82	0.38	1.81	0.17

Figure 36: Bar graph showing mean scores of variables of neuropsychological test at different doses of heroin

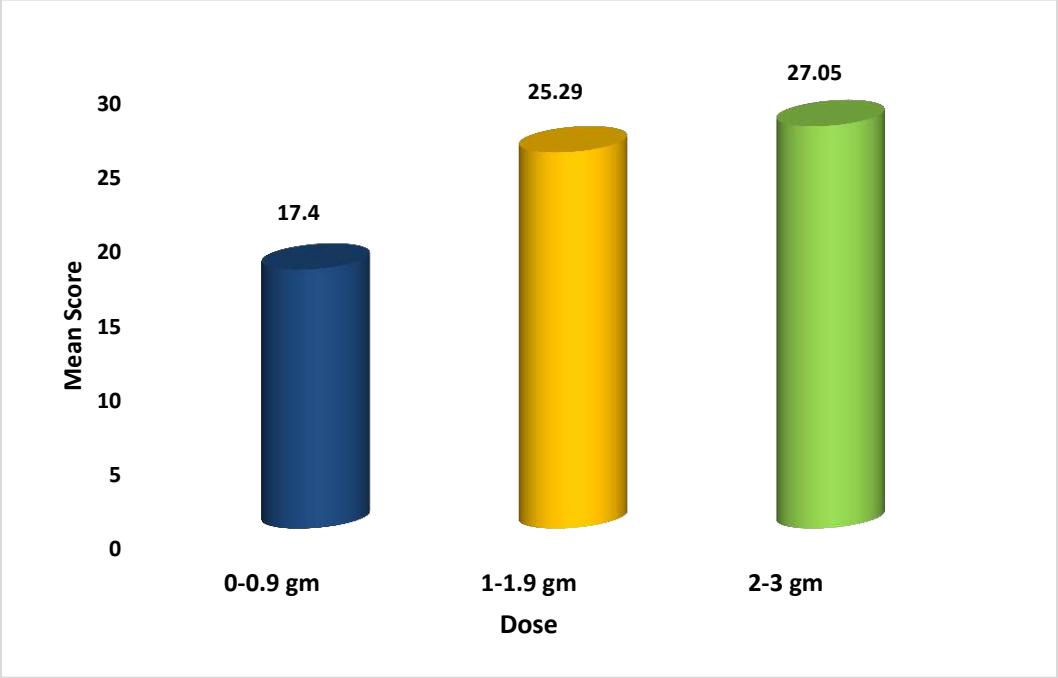


Recent memory, mental balance, attention and concentration, recognition, P/Kx100, and PQ were significantly impacted at higher doses of heroin.

Table 37: Dysfunction Rating Score at different doses of heroin

Variables	Dose						F	p-value
	0-0.9		1-1.9		2-3.0			
	Mean	SD	Mean	SD	Mean	SD		
Dysfunction Rating Score	17.40	7.38	25.29	5.50	27.05	5.21	11.67	**<0.001**

Figure 37: Bar graph showing mean dysfunction rating score at different doses of heroin



Individuals with higher doses of heroin had significantly higher Dysfunction Rating Scores.

Table 38: Mean change in variables of neuropsychological test at different doses of heroin

Variables	Dose(gm)					
	0-0.9 vs 1-1.9		0-0.9 vs 2-3.0		1-1.9 vs 2-3.0	
	Mean difference	p-value	Mean difference	p-value	Mean difference	p-value
Remote Memory	0.01	0.99	0.04	0.97	0.03	0.97
Recent Memory	-1.32	**0.001**	-0.92	**0.016**	0.39	0.25
Mental Balance	-0.52	0.19	-0.81	**0.013**	-0.28	0.37
Attention and concentration	-0.78	**0.041**	-0.86	**0.012**	-0.08	0.93
Delayed Recall	0.18	0.45	0.07	0.84	-0.10	0.59
Immediate Recall	-0.46	0.41	-0.49	0.31	-0.02	0.99
Retention of similar pair	-0.28	0.39	-0.15	0.72	0.13	0.66
Retention of dissimilar pairs	-0.39	0.39	-0.55	0.12	-0.16	0.73
Visual retention	-0.71	0.24	-0.77	0.14	-0.06	0.97
Recognition	-0.88	**0.019**	-0.70	0.051	0.18	0.69
P/Kx100	-0.97	0.11	-1.42	**0.006**	-0.45	0.37
PQ	-0.37	0.56	-0.77	0.06	-0.40	0.26
TQ Information	-0.03	0.98	0.09	0.88	0.13	0.67
TQ digit span	-0.19	0.78	-0.51	0.13	-0.32	0.25

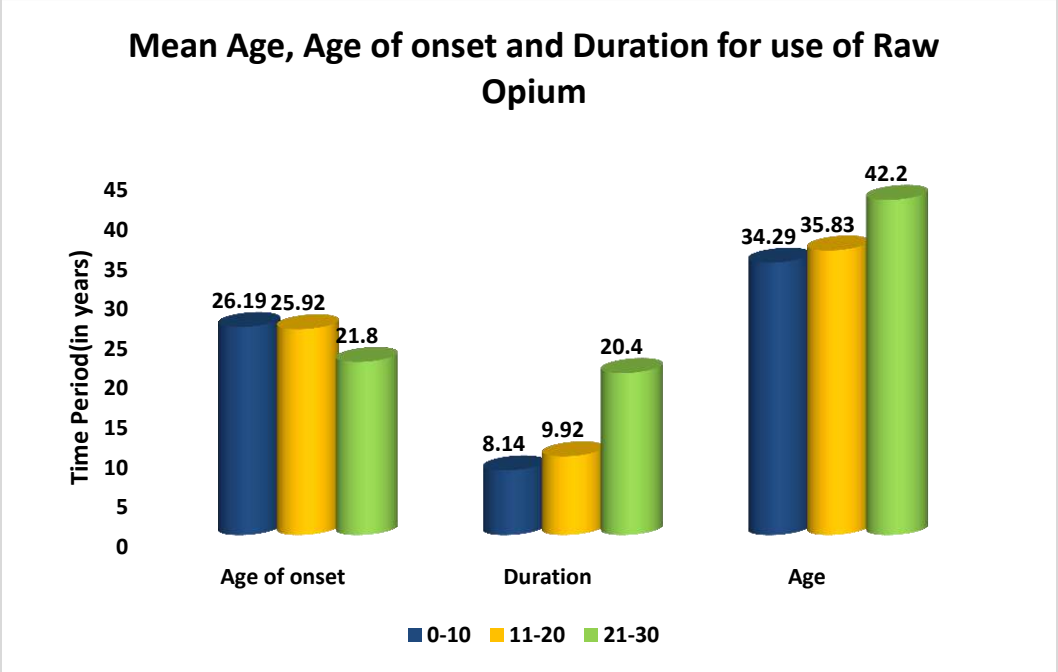
TQ arithmetic	-0.92	0.09	-0.73	0.18	0.19	0.80
TQ comprehension	0.10	0.69	0.2	0.21	0.09	0.54
PQ-VQ	0.37	0.75	-0.40	0.67	-0.77	0.09
NBT	-0.52	0.38	-0.71	0.12	-0.19	0.76
BGT	-0.25	0.17	-0.12	0.61	0.13	0.37
Dysfunction Rating Score	-7.88	**0.002**	-9.65	**<0.01**	-1.76	0.48

Impairment of recent memory, mental balance, attention and concentration, recognition, P/Kx100 and higher dysfunction rating score at the higher dose of heroin i.e. >1 gm as compared to 0-0.9 gm.

Table 39: Clinical variables according to different doses of raw opium

Variables	Dose						F	p-value
	0-10		11-20		21-30			
	Mean	SD	Mean	SD	Mean	SD		
Age	34.29	8.7	35.83	6.8	42.2	7.5	2.05	0.13
Age of onset	26.19	7.5	25.92	8.8	21.8	4.4	0.74	0.48
Duration	8.14	4.7	9.92	5.8	20.4	4.5	13.6	**<0.001**

Figure 38: Bar graph showing clinical variables according to different doses of raw opium



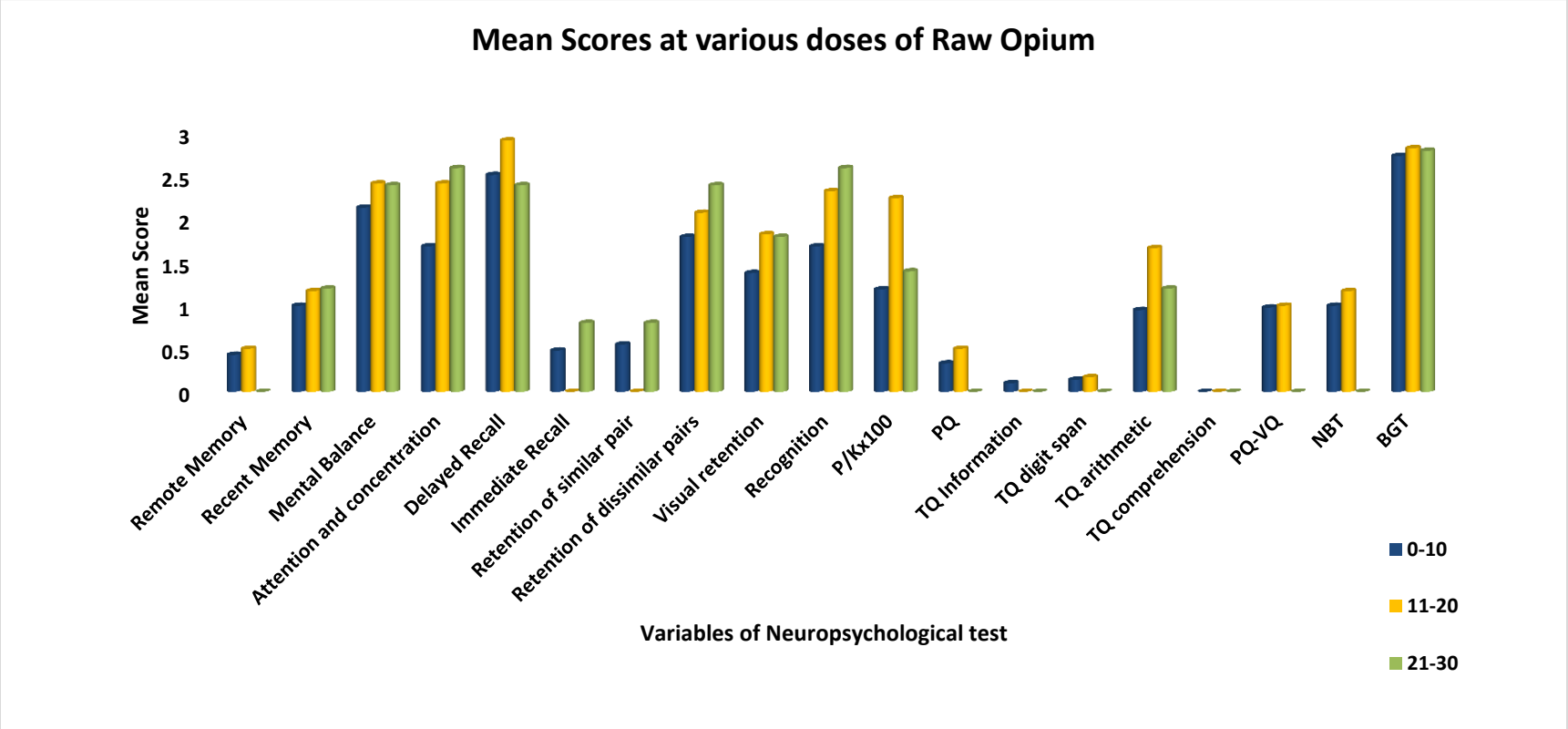
Age and age of onset did not vary significantly with the dose, whereas the duration was significantly affected by the dose.

Table 40: Mean scores of variables of neuropsychological test at different doses of raw opium

Variables	Dose(gm)						F	p-value
	0-10		11-20		21-30			
	Mean	SD	Mean	SD	Mean	SD		
Remote Memory	0.43	0.831	0.5	1.16	0	0	0.61	0.54
Recent Memory	1	1.01	1.17	1.03	1.2	1.09	0.18	0.83
Mental Balance	2.14	1.26	2.42	0.9	2.4	1.3	0.30	0.74
Attention and concentration	1.69	1.15	2.42	0.9	2.6	0.54	3.21	**0.04**
Delayed Recall	2.52	0.5	2.92	0.28	2.4	0.54	3.65	**0.03**
Immediate Recall	0.48	0.86	0	0	0.8	1.09	2.35	0.10
Retention of similar pair	0.55	1.07	0	0	0.8	1.09	2.04	0.14
Retention of dissimilar pairs	1.8	1.15	2.08	0.28	2.4	0.54	0.69	0.50
Visual retention	1.38	1.14	1.83	1.4	1.8	1.09	0.82	0.44
Recognition	1.69	1.15	2.33	0.88	2.6	0.54	2.82	0.06
P/Kx100	1.19	1.25	2.25	1.35	1.4	1.34	3.19	**0.04**
PQ	0.33	0.75	0.5	0.9	0	0	0.76	0.46
TQ Information	0.1	0.43	0	0	0	0	0.40	0.67
TQ Digit span	0.14	0.52	0.17	0.57	0	0	0.2	0.81
TQ Arithmetic	0.95	1.2	1.67	1.49	1.2	1.64	1.4	0.25

TQ Comprehension	0	0	0	0	0	0	0	0
PQ-VQ	0.98	1.35	1	1.47	0	0	1.24	0.29
NBT	1	1.01	1.17	1.03	0	0	2.70	0.07
BGT	2.74	0.44	2.83	0.38	2.8	0.44	0.24	0.78
Dysfunction rating score	21.21	6.85	25	5.34	22.4	6.91	1.54	0.22

Figure 39: Bar graph showing mean scores of variables of neuropsychological test at different doses of raw opium



Attention and concentration, delayed recall and Nahor Benson Test was impaired significantly as the dose of raw opium was increased

Table 41: Correlation of various parameters with variables of neuropsychological test in opioid users

Variables		Spearman Correlation Coefficient	p-value
Age	Duration	0.53	<0.001
	Dose	0.52	<0.001
	Recent Memory	0.16	0.04
	Immediate Memory	-0.24	0.003
	TQ Arithmetic	0.22	0.009
Age of onset	Dose	0.22	0.007
	Immediate Memory	-0.19	0.02
Dose	Duration	0.45	<0.001
	Immediate Memory	-0.25	0.003
	TQ Arithmetic	0.18	0.02
	TQ Comprehension	-0.17	0.04

Figure 40A: Correlation of age with dose and duration

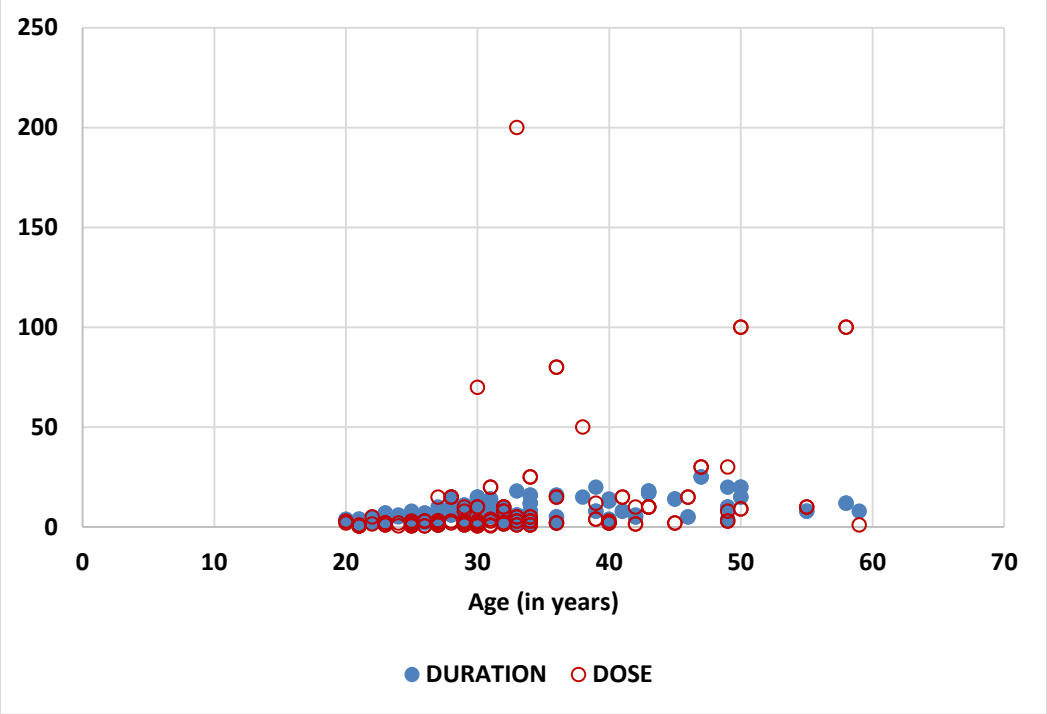


Figure 40B: Correlation of age with cognitive variables

Figure 40C: Correlation of age of onset with dose

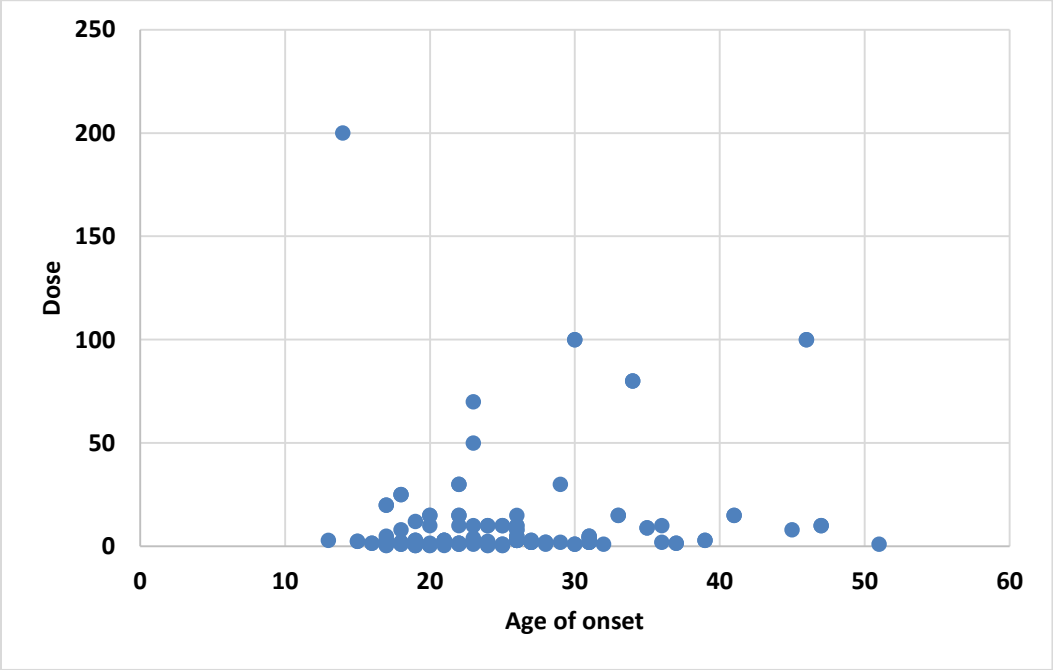


Figure 40D: Correlation of age of onset with immediate recall

Figure 40E: Correlation of dose with duration of opioid use

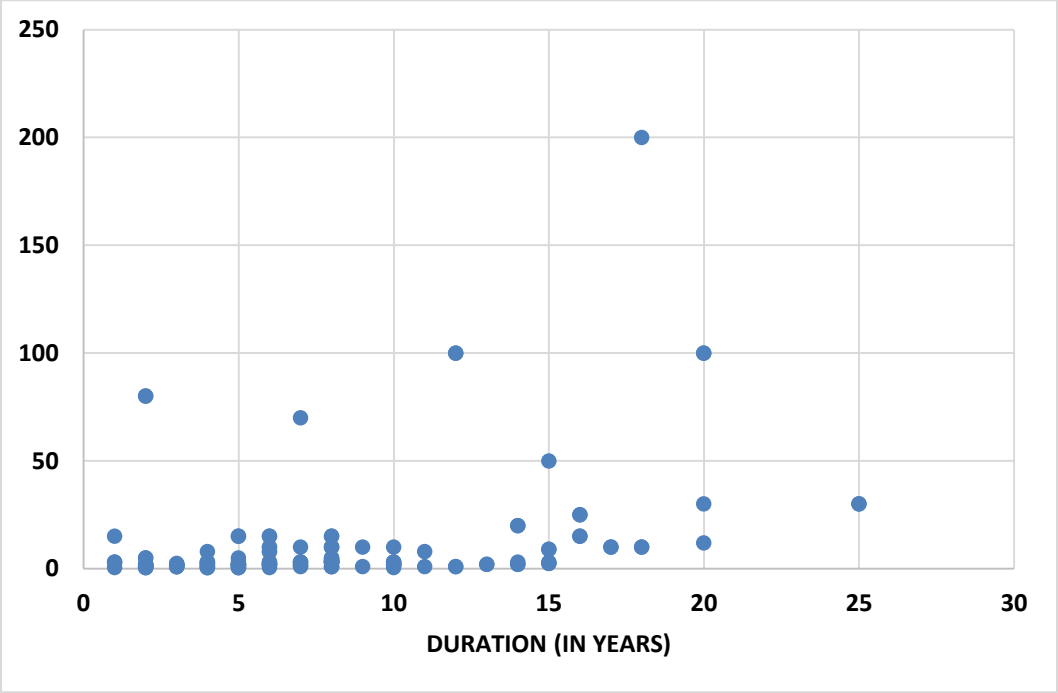
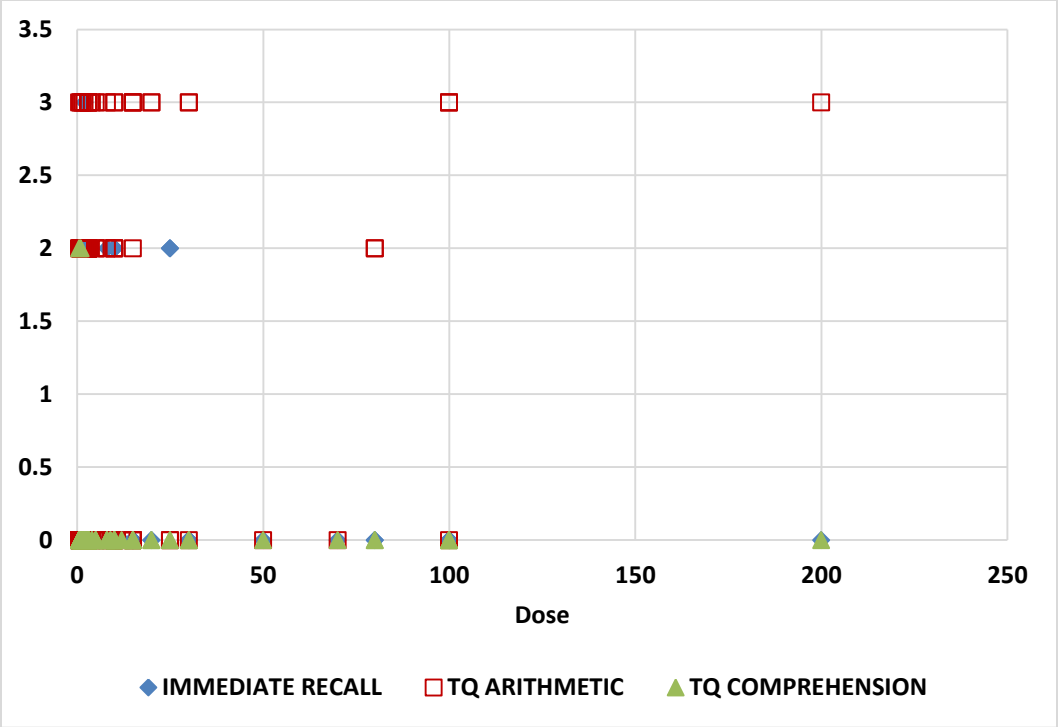


Figure 40F: Correlation of dose with cognitive variables



Older individuals used opioids for longer durations and at higher doses. Later the age of onset, the higher the dose was used. Immediate memory improved slightly with increasing age and higher doses. There were slight positive correlations between age, dose, and certain cognitive measures like recent memory and TQ arithmetic. Age of onset also showed significant correlations with dose and immediate memory, indicating the timing of onset affected these variables.

Table 42: Correlation of various parameters with variables of neuropsychological test in natural group

Variables		Spearman Correlation Coefficient	p-value
Age	Duration	0.51	<0.01
	Dose	0.52	<0.01
	PQ-VQ	-0.27	0.023
	NBT	-0.24	0.047
Age of onset	Duration	-0.24	0.04
Dose	Duration	0.41	<0.01
	Immediate Memory	-0.26	0.03
	TQ Arithmetic	0.27	0.02

Figure 41A: Correlation of age with dose and duration of opioid use

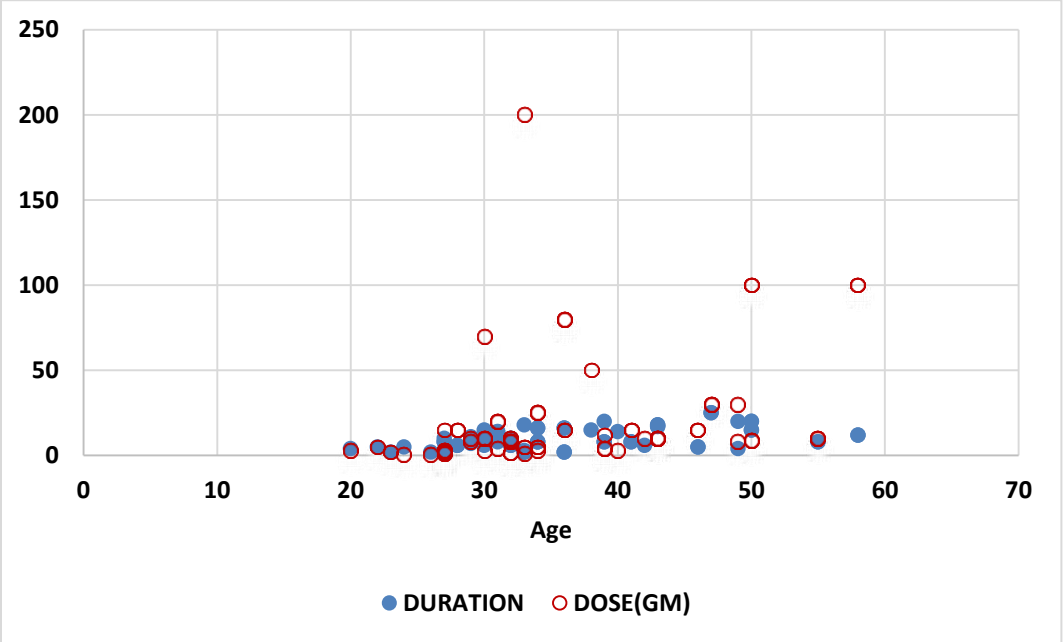


Figure 41B: Correlation of age with PQ-VQ and NBT

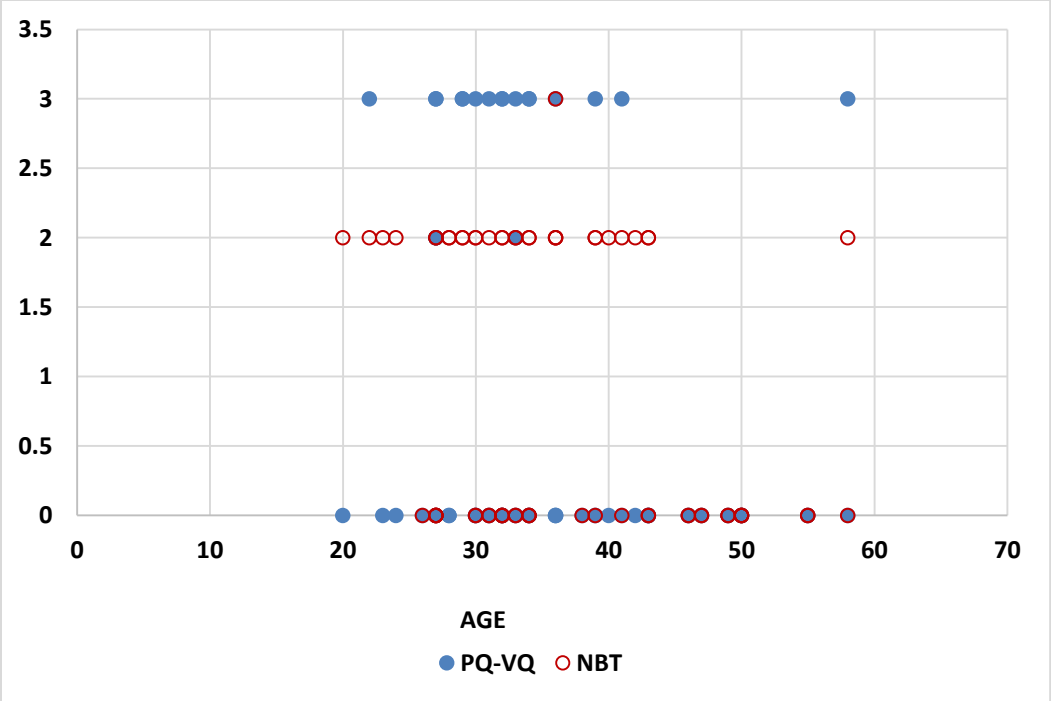


Figure 41C: Correlation of age of onset with duration of opioid use

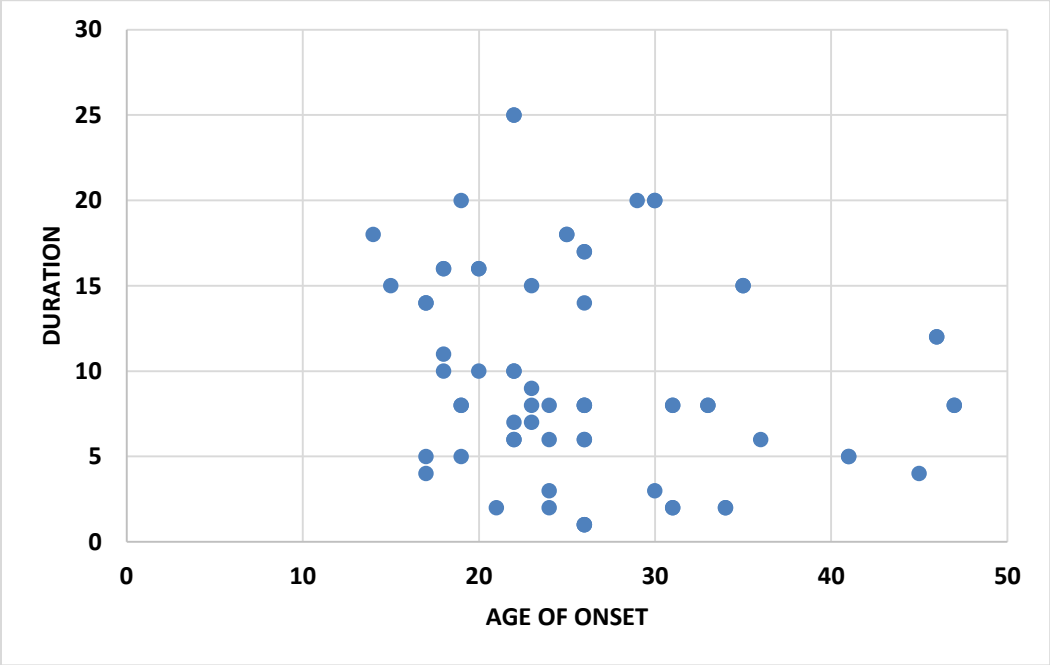


Figure 41D: Correlation of dose with duration of opioid use

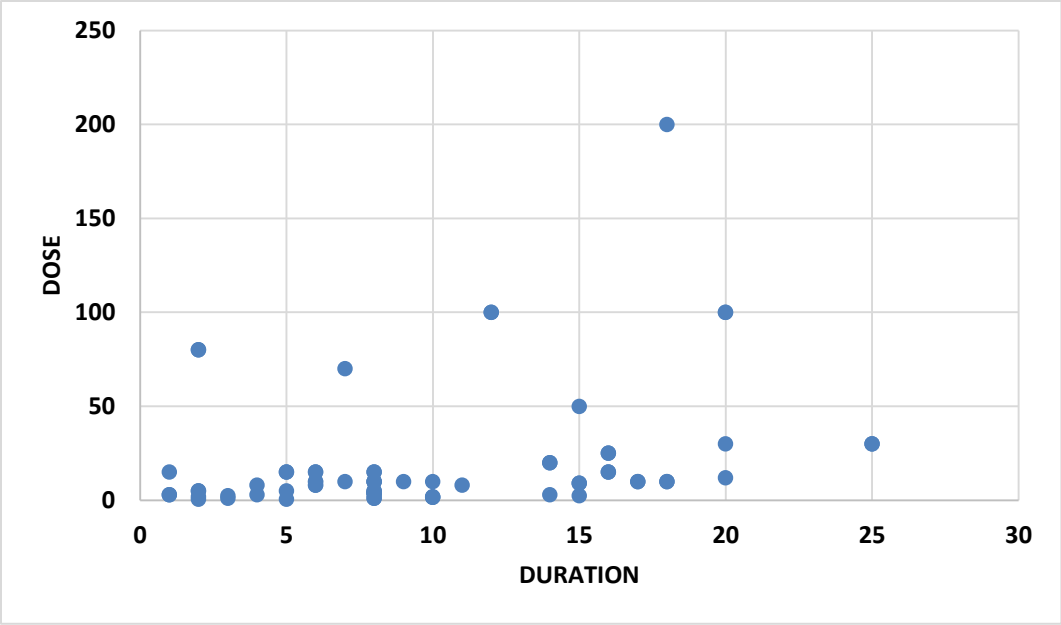
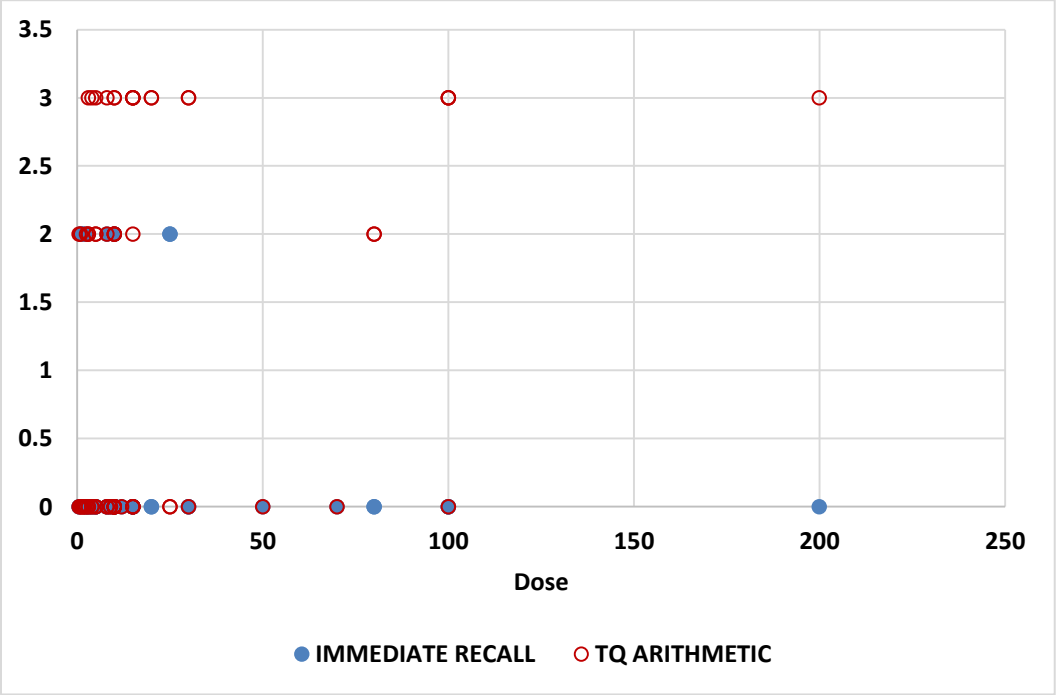


Figure 41E: Correlation of dose with immediate recall and TQ Arithmetic



Older individuals had longer durations and higher doses. Age was negatively correlated with PQ-VQ and NBT, indicating that these measures improved with increasing age, a later age of onset was associated with shorter duration in natural opioids, higher doses were associated with longer durations of use and poor arithmetic performance while higher doses showed improvement in immediate memory.

Table 43: Correlation of various parameters with variables of neuropsychological test in the synthetic group

Variables		Spearman Correlation Coefficient	p-value
Age	Duration	0.45	<0.001
	Dose	0.25	0.03
	Recent Memory	0.28	0.017
	Attention and Concentration	0.36	0.002
	Immediate Recall	-0.35	0.002
	Visual Retention	0.25	0.031
	Recognition	0.27	0.018
	PQ	0.37	0.001
	TQ Arithmetic	0.34	0.003
	NBT	0.39	0.001
	Dysfunction Rating Score	0.42	<0.01
Age of onset	Recent Memory	0.27	0.01
	Mental Balance	0.24	0.03
	Attention and Concentration	0.31	0.007
	Immediate Recall	-0.24	0.03
	PQ	0.24	0.03
	TQ Arithmetic	0.30	0.009
	NBT	0.30	0.008
	Dysfunction Rating Score	0.33	0.004
Dose	P/KX100	0.34	0.003
	PQ	0.33	0.004
	TQ Digit span	0.32	0.005
	NBT	0.24	0.036
	Dysfunction Rating Score	0.42	<0.01

Duration	Dose	0.39	0.001
	Attention and Concentration	0.26	0.028
	Immediate Recall	-0.27	0.02
	Visual Retention	0.26	0.023
	Recognition	0.26	0.022
	PQ	0.24	0.041
	TQ Information	-0.27	0.018
	NBT	0.27	0.02
	Dysfunction Rating Score	0.25	0.029

Figure 42A: Correlation of age with dose and duration

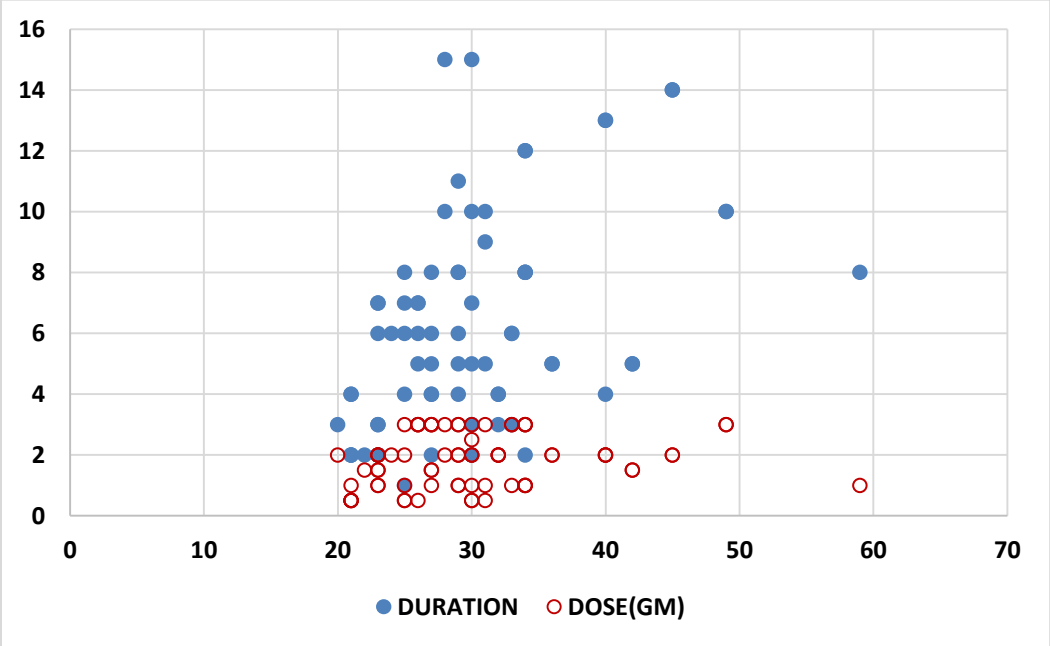


Figure 42B: Correlation of age with cognitive variables

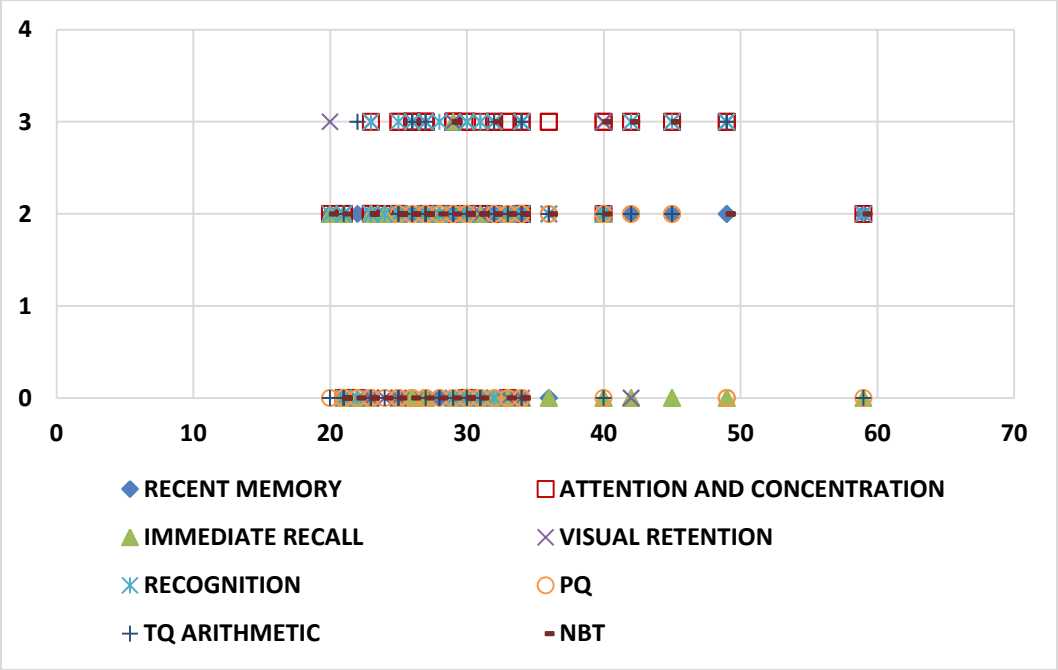


Figure 42C: Correlation of age with dysfunction rating score

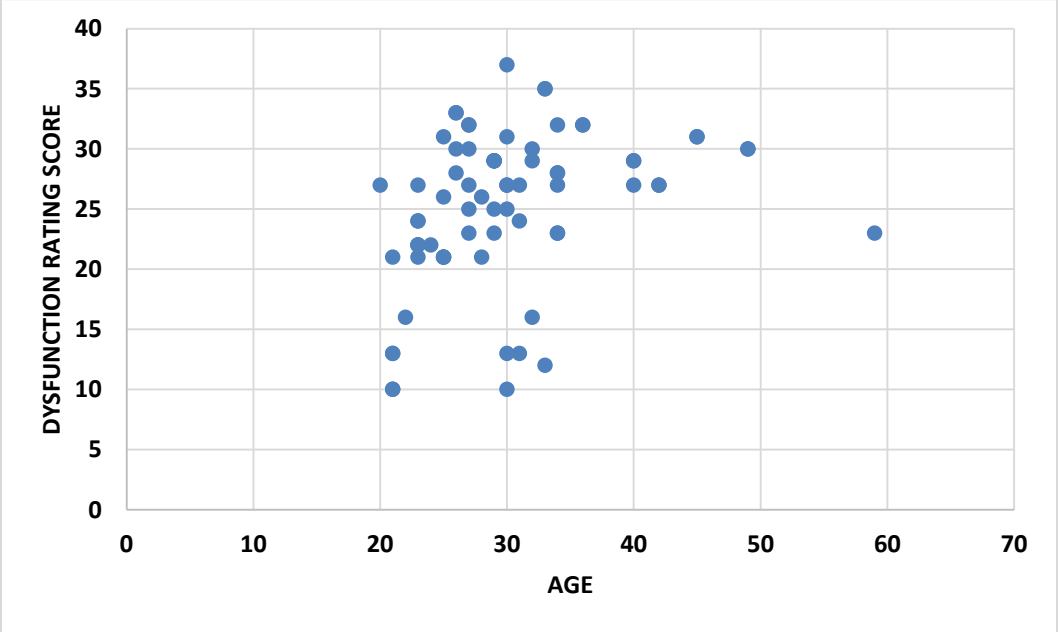


Figure 42D: Correlation of age of onset with cognitive variables

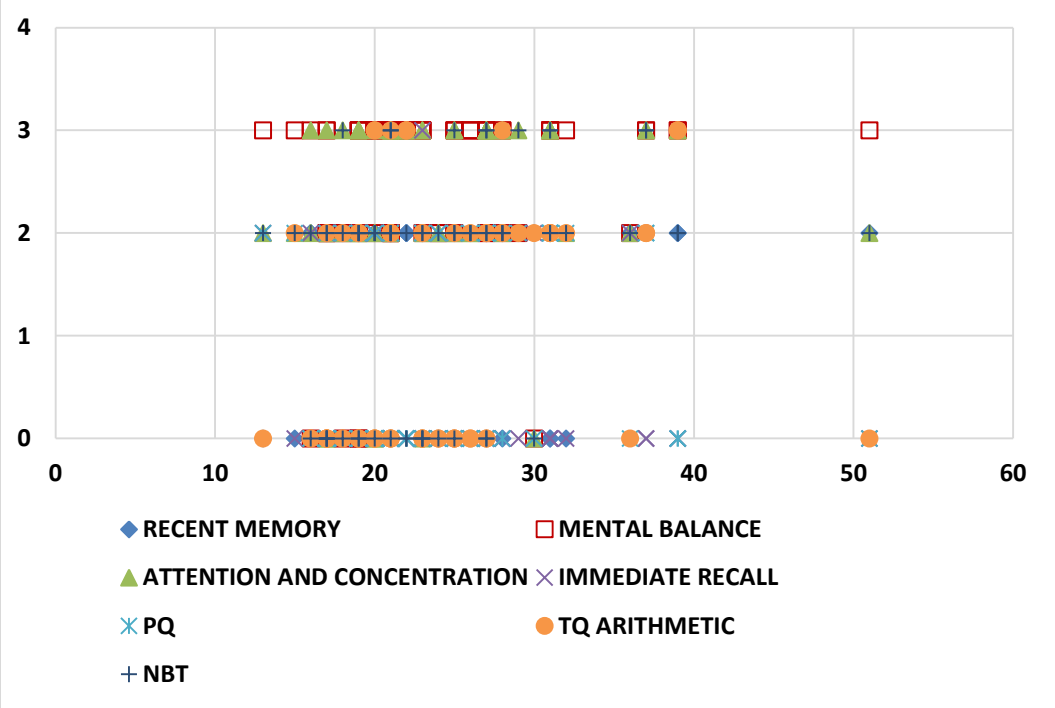


Figure 42E: Correlation of age of onset with dysfunction rating score

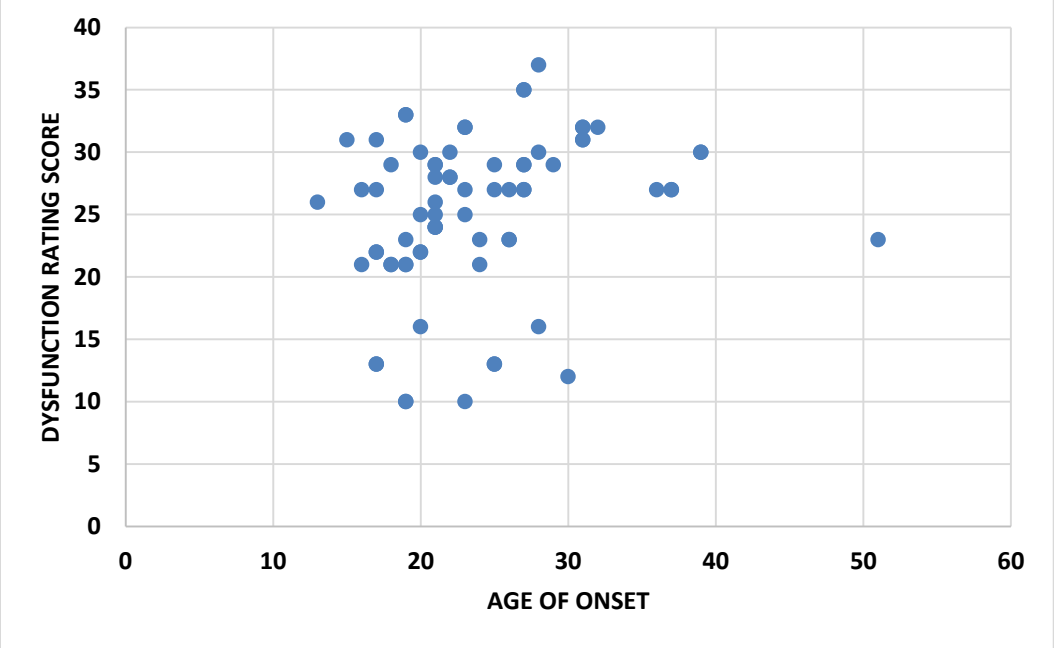


Figure 42F: Correlation of dose with cognitive variables

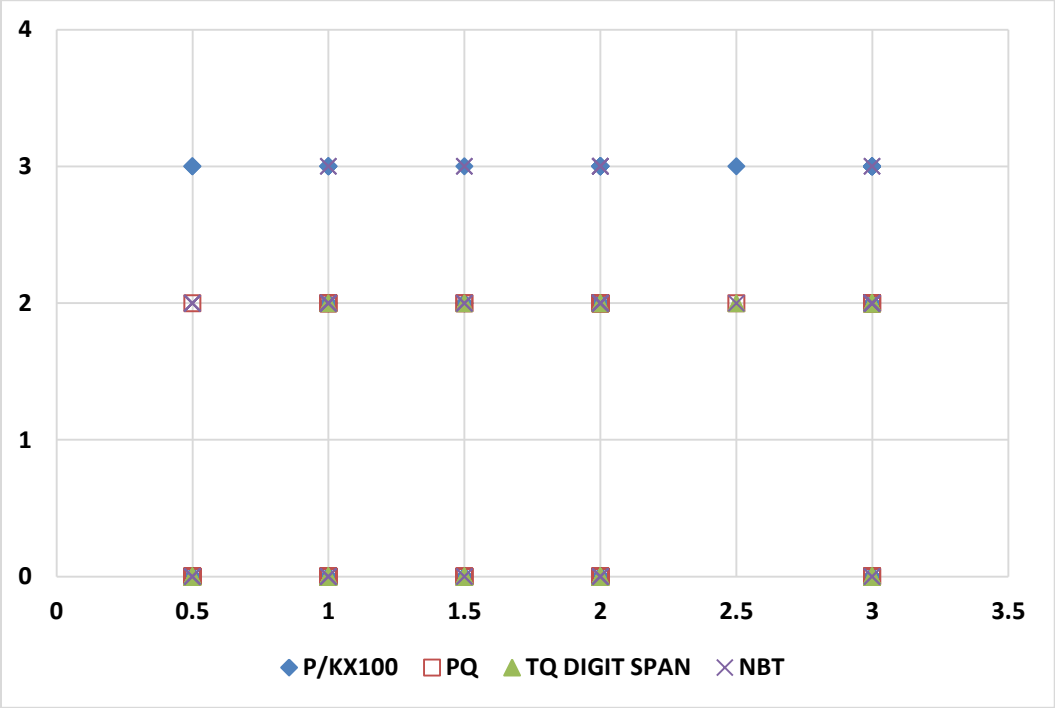


Figure 42G: Correlation of dose with dysfunction rating score

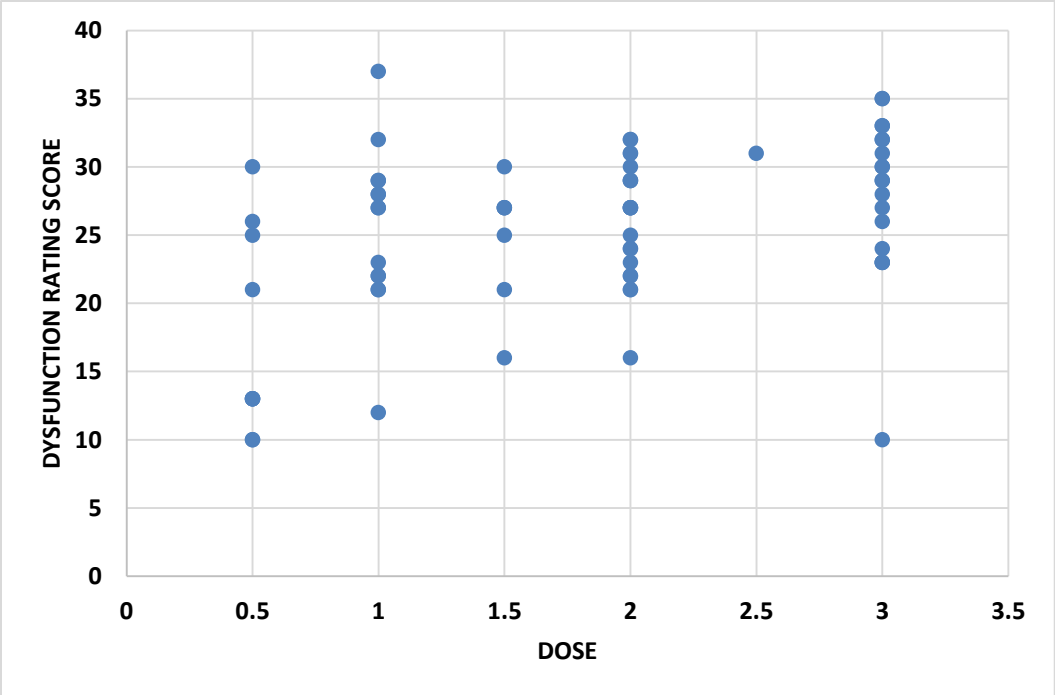


Figure 42H: Correlation of duration with dose of opioid used

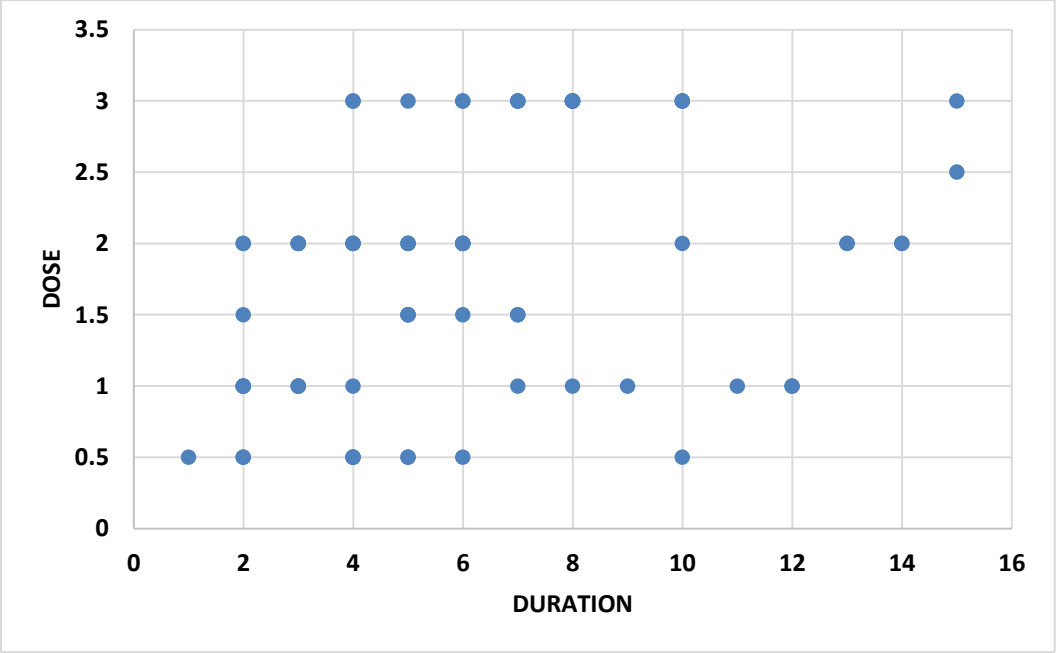


Figure 42I: Correlation of duration with cognitive variables

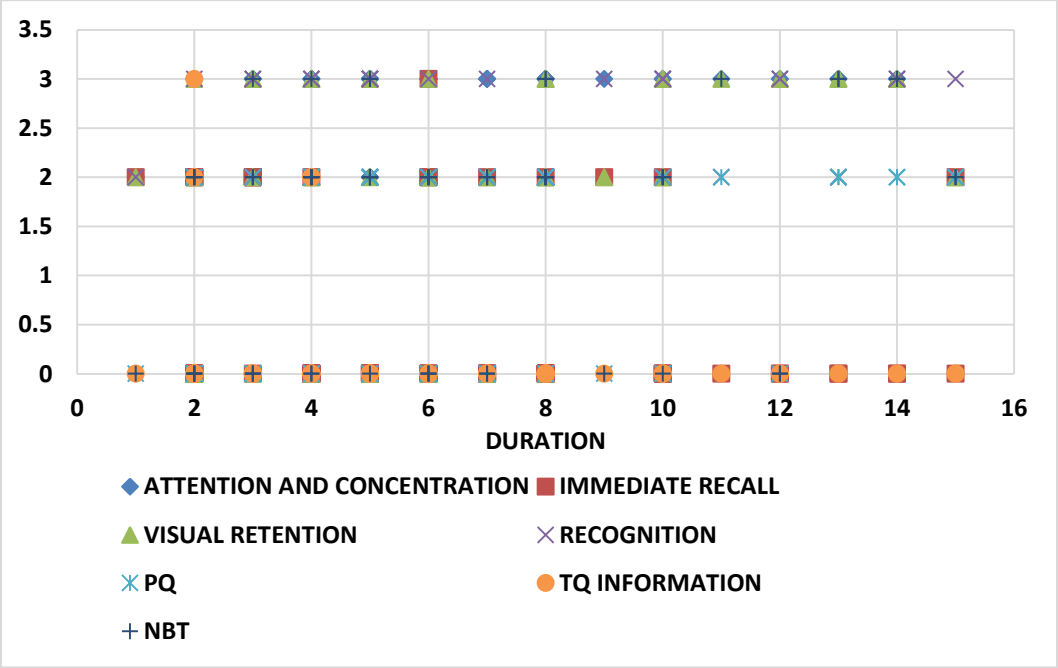
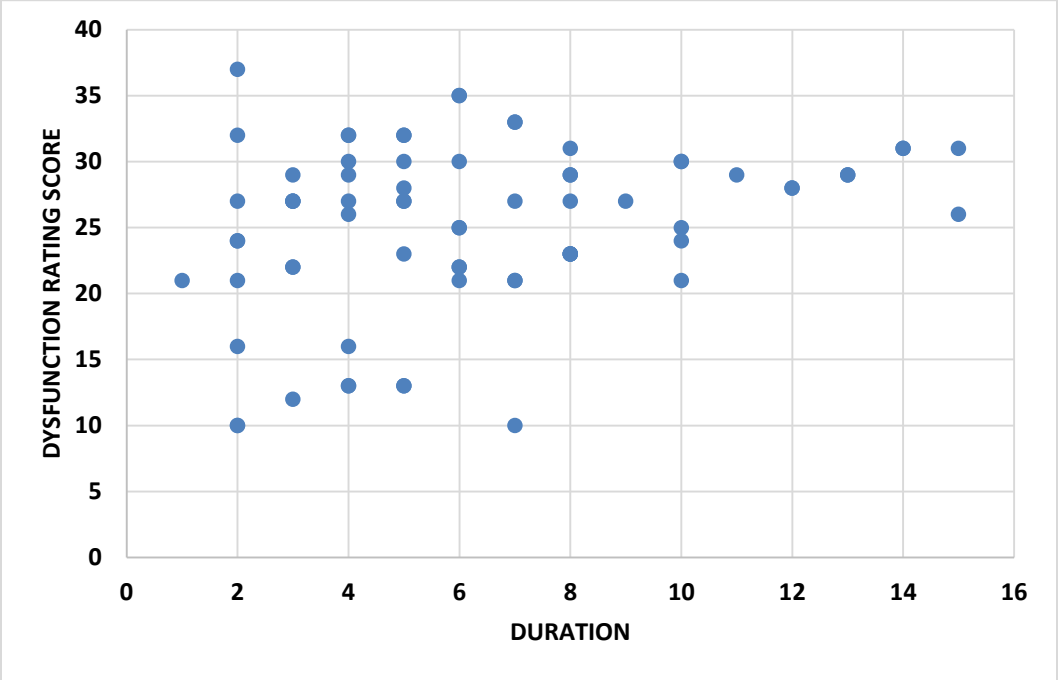


FIGURE 42J: Correlation of duration with dysfunction rating score



Show positive correlation between age and duration, age and dose and age and cognitive variables including recent memory, attention and concentration, visual retention, recognition, PQ, TQ arithmetic, NBT, dysfunction rating score and negative correlation with age and immediate memory. Age of onset showed positive correlation with recent memory, mental balance, attention and concentration, PQ, TQ arithmetic, NBT, and dysfunction rating score except for immediate recall, where it showed a negative correlation. Dose showed positive correlations with duration, P/KX100, PQ, TQ digit span, NBT, and dysfunction rating score. Duration showed a positive correlation with dose and with attention and concentration, visual retention, recognition, PQ, NBT, dysfunction rating score whereas negative correlation with immediate recall and TQ Information.

RESULTS

It was a comparative and cross-sectional study that was performed on patients seeking treatment for Opioid Dependence who presented to Deaddiction IPD/Deaddiction OPD, Department of Psychiatry, Dayanand Medical College & Hospital, Ludhiana during the period of 1 year (March 2023 to February 2024) with the patient group divided into 2: one group who used natural opioids and a second group who used synthetic opioids.

Table 1 and Figure 1 shows the distribution of study subjects with opioid dependence (n=140) into two groups: Natural opioid users (n=68, 48.6%) and Synthetic opioid users (n=72, 51.4%). Natural opioid users used raw opium (n=59, 42.1%) and poppy husk (n=9, 6.4%) and Synthetic opioid users used heroin (n=67, 47.9%) and tramadol (n=5, 3.6%).

Table 2 and Figure 2 shows the distribution and association of age group with the type of substance used. The majority of the patients seeking treatment for opioid dependence 65(46.4%) were in the age group below 30 years, followed by 47(33.6%) in 31-40 years age group, followed by 23(16.4%) in 41-50 years age group and 5(3.6%) in 51-60 years age group. The chi-square test was used to explore the association between groups and age, revealed a significant difference with the value of $\chi 2 = 17.61$ and $p = 0.001$. The mean age of natural opioid users was 36.32 ± 9.14 years and of synthetic opioid users was 30.25 ± 7.51 years.

Table 3 and Figure 3 shows the distribution and association of marital status with the type of substance used. Majority of the patients were married 75(53.6%) of which natural users were 42(61.8%) and synthetic users were 33(45.8%), followed by unmarried 57(40.7%) of which natural users were 22(32.4%) and synthetic users were 35(48.6%) and divorced 8(5.7%) of which natural users were 4(5.9%) and synthetic users were 4(5.6%). The chi-square test was used to explore the association between groups and marital status, revealed no significant difference with the value of $\chi 2 = 3.93$ and $p = 0.14$.

Table 4 and Figure 4 shows the distribution and association of education with the type of substance used. The majority of patients were educated up to Secondary school 58(41.4%) out of which natural users were 21(30.9%) and Synthetic users were 37(51.4%), followed by Graduation 40(28.6%) out of which natural users were 23(33.8%) and Synthetic users were 17(23.6%), followed by High school 15(10.7%) of which natural users were 10(14.7%) and Synthetic users were 5(6.9%), followed by Diploma 12(8.6%) of which natural users were 5(7.4%) and Synthetic users were 7(9.7%), followed by Middle school 11(7.9%) of which natural users were 7(10.3%) and Synthetic users were 4(5.6%), followed by Postgraduate 3(2.1%) of which natural users were 2(2.9%) and Synthetic users were 1(1.4%) and Primary school 1(0.7%) belonging to the synthetic group. The chi-square test was used to explore the association between groups and education, revealed no significant difference with the value of $\chi 2=9.35$ and $p=0.154$.

Table 5 and Figure 5 shows the distribution and association of occupation with the type of substance used. Majority of them were skilled workers 48(34.3%) of which natural users were 27(39.7%) and Synthetic users were 21(29.2%), followed by Semi-Professional 36(25.7%) of which natural users were 25(36.8%) and Synthetic users were 11(15.3%), followed by unemployed 33(23.6%) of which natural users were 7(10.3%) and Synthetic users were 26(36.1%), followed by Clerk 14(10.0%) of which natural users were 3(4.4%) and Synthetic users were 11(15.3%), followed by elementary jobs 5(3.6%) of which natural users were 3(4.4%) and Synthetic users were 1(1.4%), followed by Professional jobs 3(2.1%) of which natural users were 2(2.9%) and Synthetic users were 1(1.4%) and Student 1(0.7%) belonging to Synthetic group 1(1.4%). The chi-square test was used to explore the association between groups and occupation, revealed significant differences with the value of $\chi 2 =24.74$ and $p= <0.001$.

Table 6 and Figure 6 shows the distribution and association of socioeconomic status with the type of substance used. Majority of them belonged to the Upper middle class 67(47.9%) of which Natural users were 39(57.4%) and Synthetic users were 28(38.9%), followed by Lower Middle class 54(38.6%) of which Natural users were 23(33.8%) and Synthetic users were 31(43.1%), followed by Upper Lower class 16(11.4%) of which Natural users were 5(7.4%) and Synthetic users were 11(15.3%) and Upper class 3(2.1%) of which Natural users were 3(2.1%) and Synthetic users were 1(1.5%). The chi-square test was used to explore the association between groups and socioeconomic status, revealed no significant difference with the value of $\chi 2 = 5.46$ and $p = 0.141$.

Table 7 and Figure 7 shows the distribution and association of family type with the type of substance used. Maximum patients 101(72.1%) were living in a nuclear family of which natural users were 42(61.8%) and synthetic users were 59(81.9%). 36(25.7%) patients belong to joint family out of which natural users were 23(33.8%) and synthetic users were 13(18.1%). 3(2.1%) patients living alone were natural opioid users 3(4.4%). The chi-square test was used to explore the association between groups and family type, revealed significant differences with the value of $\chi 2 = 8.53$ and $p = 0.014$.

Table 8 and Figure 8 shows the mean age of onset of opioid dependence. An independent samples t-test was conducted to compare test scores in natural and synthetic groups. There was a significant difference in scores for natural group (Mean=26.47, SD=8.16) and synthetic group (Mean=23.94, SD=6.6); $t(138) = 2.008$, $p = 0.047$. The magnitude of the differences in the means (mean difference= 2.526, 95% CI: 0.039, 5.014) was small, with Cohen's d of 0.34.

Table 9 and Figure 9 shows the mean duration of opioid dependence. An independent samples t-test was conducted to compare test scores in natural and synthetic groups. The mean duration of opioid use is 8.03±5.25 years. There was significant difference in scores for natural

group (Mean=9.87, SD=6.11) and synthetic group (Mean=6.29, SD=3.52); t(105.86)= 4.20, p= <0.01. The magnitude of the differences in the means (mean difference= 3.576, 95% CI: 1.891, 5.261) was large, with Cohen's d of 0.71.

Table 10 and Figure 10 shows the distribution and association of precipitating factors with the type of substance used Most common precipitating factor was Peer pressure accounting for 88(62.9%) of which natural users were 30(44.1%) and synthetic users were 58(80.6%), followed by Interpersonal issues 38(27.1%) of which natural users were 29(42.6%) and synthetic users were 9(12.5%), followed by recreation purpose 8(5.7%) of which natural users were 5(7.4%) and synthetic users were 3(4.2%) and Loneliness 6(4.3%) of which natural users were 4(5.9%) and synthetic users were 2(2.8%). The chi-square test was used to explore the association between groups and precipitating factors, revealed a significant difference with the value of $\chi 2$=20.505 and p=<0.001.

Table 11 and Figure 11 shows the distribution and association of Comorbid nicotine use with the type of substance used. The majority of subjects used nicotine accounting for 111(79.3%), out of which natural users were 47(69.1%) and synthetic users were 64(88.9%) and 29(20.7%) did not use nicotine, out of which natural users were 21(30.9%) and synthetic users were 8(11.1%). The chi-square test was used to explore the association between groups and comorbid nicotine use, revealed a significant difference with the value of $\chi 2$=8.324 and p=0.004.

Table 12 and Figure 12 shows the distribution and association of family history of opioid dependence with the type of substance used family history of opioid dependence was present in 24(17.1%) of which natural users were 12(17.6%) and synthetic users were 12(16.7%). The majority of subjects do not have a family history of opioid dependence accounting for 116(82.9%) of which natural users were 56(82.4%) and synthetic users were 60(83.3%). The chi-square test was used to explore the association

between Groups and family history of opioid dependence, revealed no significant difference with the value of $\chi 2=0.024$ and $p=0.878$.

Table 13 and Figure 13 shows the distribution and association of family history of mental illness with the type of substance used. Family history of mental illness was present in 30(21.4%) of which natural users were 10(14.7%) and synthetic users were 20(27.8%). The majority of subjects do not have a family history of mental illness accounting for 110(78.6%) of which natural users were 58(85.3%) and synthetic users were 52(72.2%). The chi-square test was used to explore the association between groups and family History of mental illness, revealed no significant difference with the value of $\chi 2=3.54$ and $p=0.60$.

Table 14 and Figure 14 shows the scores of remote memory. 121(86.4%) subjects scored 0 of which natural users were 55(80.9%) and synthetic users were 66(91.7%), 17(12.1%) subjects scored 2 of which natural users were 11(16.2%) and synthetic users were 6(8.3%) and 2(1.4%) scored 3 of which natural users were 2(2.9%). The chi-square test was used to explore the association between groups and remote memory, revealed no significant difference with the value of $\chi 2=4.36$ and $p=0.11$.

Table 15 and Figure 15 shows the scores of recent memory. 64(45.7%) subjects scored 0 of which natural users were 33(48.5%) and synthetic users were 31(43.1%) and 76(54.3%) subjects scored 2 of which natural users were 35(51.5%) and synthetic users were 41(56.9%). The chi-square test was used to explore the association between groups and recent memory, revealed no significant difference with the value of $\chi 2=0.42$ and $p=0.516$.

Table 16 and Figure 16 shows scores of mental balance. 18(12.9%) subjects scored 0 of which natural users were 13(19.1%) and synthetic users were 5(6.9%), 33(23.6%) subjects scored 2 of which natural users were 12(17.6%) and synthetic users were 21(29.2%) and 89(63.6%) scored 3 of which natural users were 43(63.2%) and synthetic users were 46(63.9%). The chi-square test was used to explore the association

between groups and mental balance, revealed significant difference with a value of $\chi 2=6.002$ and $p=0.049$.

Table 17 and Figure 17 shows scores of attention and concentration. 20(14.3%) subjects scored 0 of which natural users were 14(20.6%) and synthetic users were 6(8.3%), 60(42.9%) subjects scored 2 of which natural users were 30(44.1%) and synthetic users were 30(41.7%) and 60(42.9%) scored 3 of which natural users were 24(35.3%) and synthetic users were 36(50%). The chi-square test was used to explore the association between groups and attention and concentration, revealed no significant difference with values of $\chi 2=5.49$ and $p=0.064$.

Table 18 and Figure 18 shows scores of delayed recall. 41(29.3%) subjects scored 2 of which natural users were 27(39.7%) and synthetic users were 14(19.4%) and 99(70.7%) scored 3 of which natural users were 41(60.3%) and synthetic users were 58(80.6%). The chi-square test was used to explore the association between groups and delayed recall, revealed a significant difference with the value of $\chi 2= 6.93$ and $p=0.008$.

Table 19 and Figure 19 shows scores of immediate recall. 107(76.4%) subjects scored 0 of which natural users were 56(82.4%) and synthetic users were 51(70.8%), 32(22.9%) scored 2 of which natural users were 12(17.6%) and synthetic users were 20(27.8%) and 1(0.7%) scored 3 who was synthetic user 1(1.4%). The chi-square test was used to explore the association between groups and immediate recall, revealed no significant difference with the value of $\chi 2= 3.12$ and $p= 0.21$.

Table 20 and Figure 20 shows scores of retention of similar pairs. 122(87.1%) subjects scored 0 of which natural users were 56(82.4%) and synthetic users were 66(91.7%), 15(10.7%) scored 2 of which natural users were 9(13.2%) and synthetic users were 6(8.3%) and 3(2.1%) scored 3 who was natural user 3(4.4%). The chi-square test was used to explore the association between groups and retention of similar pairs, revealed no significant difference with the value of $\chi 2=4.3$ and $p=0.116$.

Table 21 and Figure 21 shows scores of retention of dissimilar pairs. 18(12.9%) subjects scored 0 of which natural users were 12(17.6%) and synthetic users were 6(8.3%), 82(58.6%) scored 2 of which natural users were 37(54.4%) and synthetic users were 45(62.5%) and 40(28.6%) scored 3 of which natural users were 19(27.9%) and synthetic users were 21(29.2%). The chi-square test was used to explore the association between groups and retention of dissimilar pairs, revealed no significant difference with the value of $\chi 2=2.76$ and $p=0.25$.

Table 22 and Figure 22 shows scores of visual retention. 44(31.4%) subjects scored 0 of which natural users were 25(36.8%) and synthetic users were 19(26.4%), 59(42.1%) scored 2 of which natural users were 28(41.2%) and synthetic users were 31(43.1%) and 37(26.4%) scored 3 of which natural users were 15(22.1%) and synthetic users were 22(30.6%). The chi-square test was used to explore the association between groups and visual retention, revealed no significant difference with the value of $\chi 2= 2.18$ and $p= 0.366$.

Table 23 and Figure 23 shows scores of recognition. 22(15.7%) subjects scored 0 of which natural users were 14(20.6%) and synthetic users were 8(11.1%), 77(55%) scored 2 of which natural users were 33(48.5%) and synthetic users were 44(61.1%) and 41(29.3%) scored 3 of which natural users were 21(30.9%) and synthetic users were 20(27.8%). The chi-square test was used to explore the association between groups and recognition, revealed no significant difference with the value of $\chi 2=3.12$ and $p=0.21$.

Table 24 and Figure 24 shows scores of P/KX100. 56(40%) subjects scored 0 of which natural users were 31(45.6%) and synthetic users were 25(34.7%), 36(25.7%) scored 2 of which natural users were 17(25%) and synthetic users were 19(26.4%) and 48(34.3%) scored 3 of which natural users were 20(29.4%) and synthetic users were 28(38.9%). The chi-square test was used to explore the association between groups and

P/KX100, revealed no significant difference with the value of $\chi 2=1.97$ and $p=0.37$.

Table 25 and Figure 25 shows scores of performance quotient. 100(71.4%) subjects scored 0 of which natural users were 56(82.4%) and synthetic users were 44(61.1%) and 40(28.6%) scored 2 of which natural users were 12(17.6%) and synthetic users were 28(38.9%). The chi-square test was used to explore the association between groups and performance quotient, revealed a significant difference with the value of $\chi 2=7.732$ and $p=0.005$.

Table 26 and Figure 26 shows scores of TQ information. 133(95%) subjects scored 0 of which natural users were 66(97.1%) and synthetic users were 67(93.1%), 6(4.3%) scored 2 of which natural users were 2(2.9%) and synthetic users were 4(5.6%) and 1(0.7%) scored 3 who were synthetic users 1(1.4%). The chi-square test was used to explore the association between groups and TQ information, revealed no significant difference with the value of $\chi 2= 1.56$ and $p= 0.458$.

Table 27 and Figure 27 show scores of TQ digit span. 124(88.6%) subjects scored 0 of which natural users were 64(94.1%) and synthetic users were 60(83.3%) and 16(11.4%) scored 2 of which natural users were 4(5.9%) and synthetic users were 12(16.7%). The chi-square test was used to explore the association between groups and TQ digit span, revealed a significant difference with the value of $\chi 2= 4.018$ and $p= 0.045$.

Table 28 and Figure 28 shows scores of TQ Arithmetic. 69(49.3%) subjects scored 0 of which natural users were 36(52.9%) and synthetic users were 33(45.8%), 44(31.4%) scored 2 of which natural users were 14(20.6%) and synthetic users were 30(41.7%) and 27(19.3%) scored 3 of which natural users were 18(26.5%) and synthetic users were 9(12.5%). The chi-square test was used to explore the association between groups and TQ arithmetic, revealed a significant difference with the value of $\chi 2= 8.842$ and $p= 0.012$.

Table 29 and Figure 29 shows scores of TQ comprehension. 138(98.6%) subjects scored 0 of which natural users were 68(100%) and synthetic users were 70(97.2%) and 2(1.4%) scored 2 who were synthetic users 2(2.8%). The chi-square test was used to explore the association between groups and TQ comprehension, revealed no significant difference with the value of $\chi 2= 1.91$ and $p= 0.166$.

Table 30 and Figure 30 shows scores of PQ-VQ. 98(70%) subjects scored 0 of which natural users were 48(70.6%) and synthetic users were 50(69.4%), 6(4.3%) scored 2 of which natural users were 4(5.9%) and synthetic users were 2(2.8%) and 36(25.7%) scored 3 of which natural users were 16(23.4%) and synthetic users were 20(27.8%). The chi-square test was used to explore the association between groups and PQ-VQ, revealed no significant difference with the value of $\chi 2= 1.038$ and $p= 0.595$.

Table 31 and Figure 31 shows scores of the nahor benson test. 57(40.7%) subjects scored 0 of which natural users were 37(54.4%) and synthetic users were 20(27.8%), 71(50.7%) scored 2 of which natural users were 30(44.1%) and synthetic users were 41(56.9%) and 12(8.6%) scored 3 of which natural users were 1(1.5%) and synthetic users were 11(15.3%). The chi-square test was used to explore the association between groups and the nahor benson test, revealed a significant difference with the value of $\chi 2= 15.00$ and $p= 0.001$.

Table 32 and Figure 32 shows the scores of the Bender Gestalt Test. 28(20%) subjects scored 2 of which natural users were 17(25%) and synthetic users were 11(15.3%) and 112(80%) scored 3 of which natural users were 51(75%) and synthetic users were 61(84.7%). The chi-square test was used to explore the association between groups and the Bender Gestalt test, revealed no significant difference with the value of $\chi 2= 20.66$ and $p= 0.151$.

Table 33 and Figure 33 shows the dysfunction rating score. 37(26.4%) subjects scored <20 of which natural users were 27(39.7%) and synthetic

users were 10(13.9%) and 103(73.6%) scored >20 of which natural users were 41(60.3%) and synthetic users were 62(86.1%).

Table 34 and Figure 34 shows the mean dysfunction rating score. An independent samples t-test was conducted to compare test scores in natural and synthetic groups. There was a significant difference in scores for the natural group (Mean= 21.91, SD=6.54) and the synthetic group (Mean= 25.25, SD=6.65); t(137.10)= -3.052, p= 0.003. The magnitude of the differences in the means (mean difference= -3.338, 95% CI: -5.501, -1.176) was medium, with Cohen's d of 0.51.

Table 35 and Figure 35 shows the mean age of onset and duration at different doses of heroin. One-way analysis of variance was conducted to evaluate the null hypothesis that there is no difference in the age of onset across the different doses of heroin. In contrast, duration differs significantly across the different doses of heroin. The assumption of normality was evaluated using the Shapiro Wilk Test and found tenable for age of onset using Levene's test F= 2.48, p=0.091 and duration using Levene's test F= 1.14, p=0.324. The ANOVA results suggest that the age of onset does not differ significantly across the different doses of heroin (F=1.49, p=0.23). In contrast, the duration of opioid use differs significantly across the different doses of heroin (F=3.30, p=0.043).

Table 36 and Figure 36 shows the mean values of variables of Neuropsychological tests at different doses of heroin. There was significant difference seen in Recent memory (F=6.96, p-value=0.002), Mental balance (F=4.42, p-value=0.016), Attention and concentration (F=4.49, p-value=0.015), Recognition (F=3.97, p-value=0.023), P/KX100 (F=5.31, p-value=0.007) and Performance quotient (F=3.17, p-value=0.048).

Table 37 and Figure 37 shows the mean dysfunction rating score at different doses of heroin. At 0-0.9 grams the mean score is 17.4 ± 7.38, at 1-1.9 grams the mean score is 25.29 ± 5.50 and at 2-3 grams the mean score is 27.05 ± 5.21 with the F value= 11.67 and p-value= <0.001.

Table 38 shows the mean difference in scores of variables of Neuropsychological test at different doses of heroin with significant differences found between 0-0.9 and 2-3 grams dose in Recent memory(p-value=0.016), Mental balance(p-value=0.013), Attention and concentration(p-value=0.012), P/KX100(p-value=0.006) and in Dysfunction rating score(p-value=0.002) and between 0-0.9 and 1-1.9 grams dose in Recent memory(p-value=0.001), Attention and concentration(p-value=0.041), Recognition(p-value=0.019) and in Dysfunction rating score(p-value=<0.01).

Table 39 and Figure 38 shows clinical variables namely, mean age, duration and age of onset at different doses of raw opium. One-way analysis of variance was conducted to evaluate the null hypothesis that there is no difference in the age and age of onset across the different doses of raw. In contrast, duration differs significantly across the different doses of raw opium. For the age of onset, the independent variable dose includes 3 groups: Dose 0-10(M=26.19, SD= 7.5), Dose 11-20(M=25.92, SD= 8.8) and Dose 21-30(M=21.8, SD=4.4) and age the independent variable dose includes 3 groups: Dose 0-10(M=34.29, SD= 8.7), Dose 11-20(M=35.83, SD= 6.8) and Dose 21-30(M=42.2, SD=7.5) and for duration the independent variable dose includes 3 groups: age of onset the independent variable dose includes 3 groups: Dose 0-10(M=8.14, SD=4.7), Dose 11-20(M=9.92, SD= 5.8) and Dose 21-30(M=20.4, SD=4.5). The assumption of normality was evaluated using Shapiro Wilk Test and found tenable for age of onset using Levene's test F= 0.308, p=0.736, age of onset using Levene's test F= 1.524, p=0.227 and duration using Levene's test F= 1.252, p=0.294. The ANOVA results suggest that the age and age of onset did not differ significantly across the different doses of raw opium (F=2.05, p=0.13) and (F=0.74, p=0.48). In contrast, duration differed significantly across the different doses of raw opium (F=13.6, p=<0.001).

Table 40 and Figure 39 shows mean values of variables of neuropsychological test at different doses of raw opium with significant differences seen in Attention and concentration (F=3.21, p-value=0.04), Delayed recall (F=3.65, p-value=0.03), Recognition (F=2.82, p-value=0.06) and P/KX100 (F=3.19, p-value=0.04).

Table 41 and Figure 40A-F A Spearman's rho correlation was run to assess the relationship between sociodemographic parameters and variables of Neuropsychological test in opioid users. The distribution was not normal as observed by the Q-Q plot. There was a statistically significant, positive correlation between Age and Duration (rho=0.53, p= <0.01), Dose(rho=0.52, p= <0.01), Recent Memory(rho=0.16, p= 0.04) and TQ Arithmetic(rho=0.22, p= 0.009) and a negative correlation between Age and Immediate Memory(rho= -0.24, p= 0.003). Age of onset had a positive correlation with dose (rho=0.22, p= 0.007) and a negative correlation with immediate memory (rho= -0.19, p= 0.02). Dose had a positive correlation with duration (rho= 0.45, p= <0.01) and TQ Arithmetic(rho=0.18, p= 0.02) while a negative correlation with Immediate Memory(rho= -0.25, p= 0.003) and TQ Comprehension(rho= -0.17, p= 0.04).

Table 42 and Figure 41A-E A Spearman's rho correlation was run to assess the relationship between sociodemographic parameters and variables of Neuropsychological test in opioid users. The distribution was not normal as observed by the Q-Q plot. There was a statistically significant, positive correlation between Age and Duration (rho= 0.51, p-value= <0.01) and Age and Dose (rho= 0.52, p-value= <0.01) and a negative correlation between Age and PQ-VQ (rho= -0.27, p-value= 0.023) and Age and NBT (rho= -0.24, p-value= 0.047). Age of onset had a negative correlation with duration (rho= -0.24, p-value= 0.04). The dose had a positive correlation with duration (rho= 0.41, p-value= <0.01) and

TQ Arithmetic (rho= 0.27, p-value= 0.02) while a negative correlation with Immediate Memory (rho= -0.26, p-value= 0.03).

Table 43 and Figure 42A-J A Spearman's rho correlation was run to assess the relationship between sociodemographic parameters and variables of Neuropsychological test in opioid users. The distribution was not normal as observed by the Q-Q plot. There was a statistically significant, positive correlation between Age and Duration (rho=0.45, p= <0.001), moderate positive correlation between Age and Dose (rho= 0.25, p=0.03) and various degrees of positive correlation between Age and variables of neuropsychological test, namely Recent Memory, Attention and Concentration, Visual Retention, Recognition, PQ, TQ Arithmetic, NBT, Dysfunction Rating Score and negative correlation with age and immediate memory as p= <0.05. Age of onset showed various degrees of positive correlation with variables of the neuropsychological test, namely Recent Memory, Mental Balance, Attention and Concentration, PQ, TQ Arithmetic, NBT, and dysfunction rating score except for immediate recall, where it shows a negative correlation. Dose showed positive correlations with variables of the neuropsychological test, namely Duration, P/KX100, PQ, TQ Digit span, NBT, and dysfunction rating score as p= <0.05. Duration showed a positive correlation with dose (rho= 0.39, p=0.001) and with variables of the neuropsychological test, namely attention and concentration, visual retention, recognition, PQ, NBT, dysfunction rating score whereas negative correlation with immediate recall and TQ Information as p= <0.05. In summary, these results indicated significant relationships between age, age of onset, dose, duration, and various cognitive and dysfunction rating measures.

DISCUSSION

This study aimed to evaluate cognitive functions in opioid-dependent male patients using the PGI-BBD, a comprehensive tool that assesses multiple cognitive domains. Our study included 140 patients, divided into two groups based on the type of opioids used: natural and synthetic. Opioids have both direct and indirect effects on cognitive processes [17]. While acute opioid intake can temporarily impair some cognitive functions, these effects are not long-lasting. In contrast, long-term opioid use can have enduring effects on cognition in individuals with opioid use disorder. Numerous studies have highlighted the detrimental impact of opioids on cognitive functions. For instance, Pau et al. [32] found that heroin addiction significantly impaired impulse control. Yan et al. [64] observed that individuals with heroin addiction exhibited substantial working memory deficits and poor performance in affective decision-making tasks compared to non-users. Hekmat et al. [65] reported that opioid addiction markedly decreases cognitive flexibility, attention, and mental processing speed compared to controls. Additionally, Huili et al. [66] found that opioid users have significantly diminished attention-switching capabilities, likely related to impaired sustained attention.

The cognitive impairments induced by opioids are attributed to their adverse effects on brain structure and function, including neuronal apoptosis, gray matter loss, mitochondrial dysfunction, synaptic disturbances, and impaired neurogenesis [67]. Using various imaging modalities, such as structural MRI, DTI, and resting-state functional MRI, Upadhyay et al. [68] demonstrated that individuals with opioid use disorder exhibit bilateral volumetric loss in the amygdala, significantly reduced anisotropy in the ventral amygdala-fugal axonal pathway, uncinate fasciculus, and the internal and external capsules, as well as decreased functional connectivity in the anterior insula, nucleus accumbens, and amygdala.

Among the 140 participants in our study, 68 (48.6%) had a history of taking natural opioids which included Raw Opium (n=59, 42.1%) and Poppy Husk (n=9, 6.4%); and 72 (51.4%) were addicted to synthetic opioids which included Heroin (n=67, 47.9%) and Tramadol (n=5, 3.6%). These findings were consistent with the National Survey on Extent and Pattern of Substance Use in India 2019, which reported Heroin as the most prevalent opioid (1.14%), followed by pharmaceutical opioids (0.96%) and opium (0.52%) [11]. Similarly, the Punjab Opioid Dependence Survey(PODS) 2016 identified heroin as the most commonly used opioid (53%), followed by opium/poppy husk (33%) and pharmaceutical opioids (14%) [36]. In contrast, a study by Ajit Avasthi et. al. [35] conducted in Punjab reported lower prevalence rates, with heroin accounting for 0.19%, opium 0.24%, and poppy husk 0.51%. This highlighted the difference in addictive properties of different opioids, wherein heroin due to its rapid onset of the instantaneous surge of ecstatic pleasure makes it extremely addictive [69-71]. The availability of opioids also influence their patterns of use. Heroin, being a synthetic opioid, is more accessible in urban areas or areas with established drug trafficking routes. In contrast, natural opioids like opium and poppy husk are more prevalent in rural or agricultural regions where poppy cultivation occurs.

In our study, the majority of subjects seeking treatment were under 30 years of age (n=65, 46.4%), followed by 47 (33.6%) subjects in the 31-40 years age group, 23 (16.4%) aged between 41-50 years of age and only 5 (3.6%) were between 51-60 years of age. The age range of subjects spanned from 19 to 52 years, with a mean age of 33.20 ± 8.85 years, wherein users of natural opioids were older (mean age 36.32 ± 9.14 years) compared to users of synthetic opioids (mean age 30.25 ± 7.51 years). The difference according to the age of subjects and the type of opioid substance used by them was significant ($\chi 2=17.61$, $p=0.001$). The findings of our study were consistent with various studies by Louisa Degenhardt et. al. [9], PODS [36], Koparal et. al. [50], Saroj R et. al. [51] and

Abhishek Ghosh et. al. [57] where opioid dependence was found in the age group ranging between 18-40 years. Thus, there was a higher prevalence among younger adults. The higher prevalence of opioid use among younger adults aligns with developmental stages where experimentation and risk-taking behaviours are more common. Early initiation of substance use leads to dependence issues becoming apparent earlier in life. Younger individuals may be more susceptible to peer influence and societal pressures associated with drug use, which could explain why synthetic opioids, such as heroin, are more prevalent in this age group compared to natural opioids.

Regarding educational attainment, the majority of participants were literate and had completed secondary school or higher education, findings which were consistent with PODS [36]. There was no significant difference in education of the subject and the type of opioid used by them. This finding may be attributed to early initiation of drug use, which likely led to a decreased interest in academics and consequently, early school dropout. Our study also revealed that most of the subjects were married 75(53.6%), which correlated with findings of PODS[36] where 54% of subjects were married. The difference according to the marital status of the subject and the type of opioid used by them was not significant. A higher proportion of married individuals seeking treatment can be attributed to marital and family pressures prompting individuals to seek help, and support from spouses or family members in recognizing the problem and encouraging treatment. These findings were in accordance with the results of a study conducted by Koparal et al. [50], Saroj R et. al. [51], Gharahi et al. [52], where the difference between the two groups regarding the educational status and marital status was not found to be significant.

In terms of occupation, a substantial number of participants (75.7%) were employed, comparable to findings in PODS [36]. The most common occupations included skilled worker (13%); Transport worker (14%) clerical jobs/businessmen (15%); Farmer (21%); and unskilled

worker/labourer (27%). The difference present according to the occupation of the subject and the type of opioid used by them was highly significant (p= <0.01). The subjects who were semi-professionals (n=25) and skilled (n=27) used natural opioids and subjects who were unemployed (n=26) used synthetic opioids, predominantly heroin. These results align with study by Koparal et al., [50] where a significant difference was found to be present between the two groups regarding employment status (p=0.01). Our findings contrasted with the study performed by Saroj R et. al [51] where the occupation of the subject was not associated with the type of substance used by them. A significant number of employed individuals seeking treatment could be due to occupational stress, the availability of disposable income facilitating substance use, and workplace programs and healthcare benefits that encourage treatment seeking. Differences in opioid type use based on occupation may be tied to access and availability of different types of opioids in various work environments and stress and coping mechanisms differing by job type.

Regarding socioeconomic status, the difference between the groups and the type of opioid used by them was not significant ($\chi 2=5.46$, p=0.141). Most of the subjects belonged Upper Middle class(n=67) who predominantly used natural opioids (n=39, 57.4%). The use of synthetic opioids was predominantly seen in the lower middle-class subjects (n=31, 43.1%). These findings were similar to that of Saroj R et. al. [51] and Koparal et al. [50]. In PODS [36] heroin was the most commonly used opioid belonging to the lower middle class, which was consistent with our study. No significant difference in socioeconomic status and type of opioid use may indicate widespread accessibility of both natural and synthetic opioids across different economic strata and the pervasive nature of opioid dependence that cuts across socioeconomic boundaries.

In our study, the family structure also had a significant association with the type of opioids used ($\chi 2=8.53$, p=0.014). Opioids were predominantly used by the subjects belonging to the nuclear family (n=101, 72.1%) out of

which synthetic opioids (n=59, 81.9%) were predominantly used and subjects from the joint family mainly used natural opioids (n=23, 33.8%). These findings contrasted with the study conducted by Saroj R et. al [51], where the association between the groups using different types of opioids and the family type was not significant. The predominance of opioid use among nuclear family members, especially synthetic opioids, can be related to less social control and monitoring in nuclear families compared to joint families, and increased stress and responsibility in nuclear family settings prompting substance use [72].

In our study, the mean age of onset of opioid dependence in subjects using natural opioids was 26.47 ± 8.16 years and synthetic opioids were 23.94 ± 6.6 years. The difference in scores for the natural group and synthetic group was significant (t (138) = 2.008, p= 0.047). The magnitude of the differences in the means (mean difference= 2.526, 95% CI: 0.039, 5.014) was small, with Cohen's d of 0.34. Findings of the study conducted by Saroj R et. al. [51], where the mean age of onset of opioid use was 22.05 ± 4.5 years, and Mitrović SM et. al. [73], where examinees reported that their first heroin use was around the age of 19 (M=18.9; SD=2.49), correlated with our study. The earlier age of onset of opioid dependence among synthetic opioid users compared to natural opioid users can be explained by factors such as higher potency, immediate effects, accessibility, social influences, and risk-taking behaviours.

In our study, the difference in the mean duration of opioid use and the type of opioid used by them was highly significant. The mean duration of subjects using natural opioids was 9.87 ± 6.11 years and synthetic opioids were 6.29 ± 3.52 years with t (105.86) = 4.20, p= <0.01. The magnitude of the differences in the means (mean difference= 3.576, 95% CI: 1.891, 5.261) was large, with Cohen's d of 0.71. These findings were consistent with the study of Saroj R et. al. [51] where the mean duration for opioid dependence was 6.3 ±6.4 years. In a study by Mitrović SM et. al. [73], examinees with longer duration of opioid use started with heroin abuse at

a younger age (F4.716; df=0.012). The longer mean duration of use among natural opioid users can be attributed to factors such as chronic medical use, lower potency, and fewer interruptions due to legal and health issues. In contrast, the shorter duration among synthetic opioid users is influenced by higher potency, greater risk of overdose, and legal consequences [74]. These factors, combined with statistical evidence of a significant difference, provide a comprehensive justification for the observed differences in opioid use duration.

In our study, precipitating factors for opioid use varied significantly between the two groups ($\chi 2$= 20.505, p=<0.001). The most common precipitating factor for opioid use was peer pressure 88(62.9%) of which 30(44.1%) used natural opioids and 58(80.6%) used synthetic opioids, followed by Interpersonal issues 38(27.1%) of which 29(42.6%) used natural opioids and 9(12.5%) used synthetic opioids. Our findings corroborated with those of PODS [36] where 75% used opioids due to peer influence. Peer pressure as a leading factor for opioid use, especially synthetic opioids, can be explained by the strong influence of social circles and peer groups in substance initiation and use. Social media and cultural references make opioid use appear more acceptable or desirable among younger individuals [72,75].

In our study, 111 subjects (79.3%) exhibited comorbid nicotine use along with opioid use. The difference between the type of opioid used by two groups and the presence of comorbid nicotine use (p=0.004) was observed to be significant. Among subjects without comorbid nicotine use, the majority (n=21) used natural opioids. Conversely, among those with comorbid nicotine use, the majority (n=64) used synthetic opioids. Both nicotine and synthetic opioids, such as heroin, heavily engage the brain's reward and reinforcement pathways. The concurrent use of opioids and nicotine can enhance subjective positive effects and satisfaction from drug use, alleviate withdrawal symptoms for both substances and serve as a substitute when one drug is unavailable [76,77]. This combined use often

results in increased consumption of one or both substances due to priming, extended reinforcement, and cross-tolerance mechanisms [78-80]. Polysubstance use amplifies reinforcement because opioids and nicotine stimulate similar reward pathways, including the dopaminergic, cannabinoid, and nicotinic-acetylcholine (nAChR) systems [81,82]. Due to these related metabolic and neural processes, smoking can increase opioid use, including opioid replacement medications [83]. Simultaneously, opioid use, including prescription replacement drugs, can reinforce smoking behaviours. [84,85]. Thus, the combined use of these substances enhances the pleasurable effects, leading to a preference for synthetic opioids among nicotine users. Also, nicotine use is often associated with specific behavioural patterns and social circles that might also favour synthetic opioids. These substances are likely more readily available or preferred in environments where nicotine use is common. Additionally, individuals using nicotine may be seeking to self-medicate underlying issues such as stress or anxiety, therefore, synthetic opioids, which are often perceived as more potent, may be chosen to address these psychological needs more effectively than natural opioids [86].

Our study found no significant difference between the type of opioid used and the presence of a family history of opioid dependence or mental illness. While a family history of opioid dependence or mental illness suggests a genetic predisposition to substance use, it does not necessarily determine the specific type of opioid used. Environmental factors, personal experiences, and social influences may play a more decisive role in the choice of substance, as well as the availability of different types of opioids, influenced by geographic and socio-economic factors, often overshadows genetic predispositions [87]. Furthermore, the choice of opioid type might be driven more by the perceived effectiveness of the substance in coping with specific circumstances rather than familial patterns [88]. Familial influence may not be specific to the type of opioid but rather to substance use in general. This non-specificity indicates that while

individuals with a family history are more likely to use substances, the particular type of opioid they choose is more likely influenced by external factors than by familial patterns.

Memory is a fundamental component of cognitive functions. In this study, the difference between the scores of remote and recent memory and the type of opioid used by the two groups was not significant. Similar findings were from the study by Koparal et al. [50], whereas they contrasted with the study conducted by Sanjari Moghaddam H et. al. [55] and Warner NS et. al. [59], where a significant difference was found. The lack of significant differences in remote and recent memory scores between natural and synthetic opioid users in our study can be attributed to the uniform impact of both opioid types on memory functions. Differences observed in other studies can be explained by variations in study design, comparison groups, and the focus on longitudinal versus cross-sectional data. These factors collectively support the justification for our study's findings.

In our study, the difference in the scores of mental balance of subjects and the type of opioid used by them was found to be significant (p=0.049). As in subjects with a mental balance score of 0, the maximum (n=13) used natural opioids but in subjects who had a mental balance score of 3, the majority (n=46) used synthetic opioids. The significant difference in mental balance scores between natural and synthetic opioid users is likely due to the higher potency and neurotoxic effects of synthetic opioids, more intense patterns of use, greater underlying psychological issues, and the social environments associated with synthetic opioid use [74,89]. These factors collectively contribute to poorer mental balance among synthetic opioid users compared to those using natural opioids.

In our study, there was no significant difference in the scores of attention and concentration between subjects using natural opioids and those using synthetic opioids. These findings were consistent with the study by Rapeli et al. [44]. However, they contrasted with the findings of Sara L. Kroll et al. [49], Saroj R et al. [51] and Sanjari Moghaddam H et al. [55], where attention

scores differed significantly among groups. Brain structure abnormalities are found in neural regions and networks that are crucial for executive and attentional cognitive functions, such as the dorsolateral prefrontal cortex, anterior cingulate cortex, and medial-temporal cortices. [90,91]. The lack of significant differences in attention and concentration scores between natural and synthetic opioid users in our study is likely due to the uniform impact of both types of opioids on these cognitive domains. In contrast, the differences observed in other studies may be attributed to variations in study design, comparison groups, severity of addiction, and assessment tools. These factors collectively explain the discrepancies in findings across different research studies.

In our study, the difference found in the scores of delayed recall and the type of opioid used by the two groups was significant (p=0.008). As in subjects with a delayed recall score of 2, the maximum (n=27) used natural opioids but in subjects who had a delayed recall score of 3, the majority (n=58) used synthetic opioids. Similar were the findings of S.C. Wollman et. al. [48], Koparal et al. [50], Saroj R et. al. [51], Sanjari Moghaddam H et. al. [55], and Tian et al. [58] where a significant difference was found with p= <0.05. Our findings contrasted with the study conducted by Rapeli et. al. [44] where there was no significant difference found. The significant differences in delayed recall scores between natural and synthetic opioid users can be attributed to the higher potency and neurotoxic effects of synthetic opioids, which lead to greater cognitive impairments [74,89]. The consistency of these findings with other studies supports the conclusion that synthetic opioids have a more profound impact on delayed recall and memory functions. Differences in study design and comparison groups can account for the contrasting findings in the study.

In our study, the difference in the scores of immediate recall and the type of opioid used by the two groups was not significant. These findings were consistent with the study of Rapeli et. al. [44] where there was no significant

difference found. Whereas, these contrasted with the findings in studies by S.C. Wollman et. al. [48], Saroj R et. al. [51], and Sanjari Moghaddam H et. al. [55], where a significant difference was found. The lack of significant differences in immediate recall scores between natural and synthetic opioid users in our study was likely due to the similar impact of both types of opioids on short-term memory. The consistency with Rapeli et al. [44] supports this notion. Differences in study design, sample characteristics, and sensitivity of cognitive assessments in other studies by S.C. Wollman et. al. [48], Saroj R et al. [51], and Sanjari Moghaddam H et. al. [55] can explain the contrasting findings.

In our study, the difference in the scores of retention for similar pairs and dissimilar pairs and the type of opioid used by the two groups was not significant. Also, the difference in the scores of visual retention and recognition tests and the type of opioids used by the two groups was not significant. A study by Sanjari Moghaddam H et. al. [55] showed similar findings. We found contrasting evidence in the study of SC. Wollman et.al. [48] where a significant difference was present between the groups ($\chi 2$= 6.942, p=0.000). The lack of significant differences in the scores of retention for similar or dissimilar pairs, visual retention, and recognition tests between natural and synthetic opioid users in our study suggests a uniform impact of both opioid types on these specific cognitive functions. The consistency with the findings of Sanjari Moghaddam H et al. [55] supports this notion. The differences observed in the study by SC. Wollman et al. [48] may be attributed to variations in study design, population characteristics, and the sensitivity of cognitive assessment tools used. These factors collectively explain the discrepancies in findings across different research studies.

In our study, the difference between the scores of P/KX100 and the type of opioids used by subjects was not significant, whereas the difference present in the scores of PQ for subjects and the type of opioid used by them was significant (p=0.005). Subjects with PQ score of 0 had a

maximum (n=56) use of natural opioids but in subjects who had a PQ score of 2, the majority (n=28) used synthetic opioids. The findings were consistent with other studies namely, Sanjari Moghaddam H et.al. [55] (p=<0.0001) and S.C. Wollman et. al. [48] on block design (z=4.788, p=0.000) and on DSST (z=7.713, p=0.000). The significant difference in PQ scores between natural and synthetic opioid users in our study is likely due to the higher potency and more severe neurocognitive impact of synthetic opioids [74,89]. The consistency of these findings with previous research by Sanjari Moghaddam H et. al. [55] and S.C. Wollman et. al. [48] further supports the conclusion that synthetic opioids lead to greater cognitive impairments in performance-related tasks. Variations in neuropsychological effects and the specific cognitive domains affected by different types of opioids also contribute to these differences.

In our study, the difference in the scores of TQ information and the type of opioid used by subjects was not significant. Whereas, the difference in the scores of the TQ digit span of subjects and the type of opioid used by them was significant (p=0.045). Subjects with TQ digit span score of 0 had a maximum (n=64) use of natural opioids but in subjects who had a TQ digit span score of 2, the majority (n=12) used synthetic opioids. Our findings were consistent with that of the study conducted by S.C. Wollman et. al. [48]. In the present study, the difference in the scores of the TQ Arithmetic of subjects and the type of opioid used by them was significant (p=0.012). Subjects with TQ Arithmetic score of 0 had a maximum (n=36) use of natural opioids but in subjects who had a TQ Arithmetic score of 2, the majority (n=30) used synthetic opioids. The difference in the scores of TQ Comprehension and PQ-VQ, and type of opioid used by the two groups was not significant. The significant differences in TQ Digit Span and TQ Arithmetic scores between natural and synthetic opioid users can be attributed to the higher cognitive load, attention, and working memory demands of these tests, which are more severely impacted by synthetic opioids. The lack of significant differences in TQ Information, TQ

Comprehension, and PQ-VQ scores suggests that these cognitive domains are similarly affected by both types of opioids, reflecting a uniform impact on general knowledge, verbal comprehension, and overall cognitive functioning.

In our study, the difference in the scores of NBT and the type of opioid used by the two groups was significant (p=0.001). As in subjects with NBT score of 0, the maximum (n=37) used substance was natural opioids but in subjects who had NBT scores 2 and 3, the majority (n=41, 11; respectively) used synthetic opioids. The difference in the scores of BGT and the type of opioid used by the two groups was not significant. Out of subjects with BGT score of 3 (n=112, 80%), 61(84.7%) used synthetic opioids and 51(75%) used natural opioids. In a study by Ghosh A. et. al. [61], Both HCV(+) and HCV(–) subjects with opioid dependence exhibited significantly poorer performance than healthy controls on the Iowa Gambling Task (IGT) and the N-Back Test (NBT) for visual working memory. This suggests overlapping cognitive dysfunctions in the areas of cognitive impulsivity, decision-making, and visual working memory. Synthetic opioids significantly impair visual working memory and cognitive impulsivity due to their higher potency and neurotoxic effects [74,89], as evidenced by higher NBT scores among synthetic opioid users in our study. The BGT results indicate that visual-motor integration and perceptual-motor skills were similarly affected by both natural and synthetic opioids, leading to no significant differences in BGT scores. These factors collectively justify the significant differences observed in NBT scores and the lack of significant differences in BGT scores between natural and synthetic opioid users in our study.

In our study, subjects with dysfunction rating score <20, maximum (n=27) use of natural opioids was found but in subjects who had a Dysfunction rating score >20, the majority (n=62) used synthetic opioids. There was a significant difference in the mean dysfunction rating score for natural group (Mean=21.91, SD=6.54) and synthetic group (Mean=25.25,

SD=6.65); t (137.10) = -3.052, p= 0.003. The magnitude of the differences in the means (mean difference= -3.338, 95% CI: -5.501, -1.176) was medium, with Cohen's d of 0.51, indicating a meaningful difference in dysfunction levels. The significant differences in Dysfunction Rating Scores between natural and synthetic opioid users can be attributed to the higher potency and greater neurotoxic effects of synthetic opioids affecting numerous neural circuits, leading to more severe cognitive and functional impairments [74,89]. The higher Dysfunction Rating Scores among synthetic opioid users reflect the substantial impact of these substances on overall cognitive functioning and daily life [17,92]. Various studies have found significant cognitive impairment in opioid users, predominantly among synthetic users. Brain structure abnormalities are observed in neural regions and networks associated with executive and attentional cognitive functions, including the dorsolateral prefrontal cortex, anterior cingulate cortex, and medial-temporal cortices [93]. Chronic heroin-dependent individuals have demonstrated reductions in grey matter within the left gyrus and the cingulate gyrus. [93].

In a study by Sanjari Moghaddam H et.al. [55], the most impacted cognitive functions in patients with opium use disorder were identified by DBT and DSST. In patients with disorders due to opioid use, a significant correlation was found between the duration of opium use with the DBT score (r = 0.483 and P value < 0.01) and DSST score (r = 0.542 and P value < 0.01). DBT score was correlated with opium use quantity (r = −0.385, p-value < 0.05), i.e. attention is affected by both the dose as well as the duration of opioid use. These findings were consistent with our study where attention and concentration were significantly and positively correlated with the duration (rho= 0.26, p=0.028). It was also found that attention and concentration were significantly correlated with the age of the subject and the age of onset of synthetic opioid use in the subject. These findings indicated that information-processing speed and working memory were the most affected areas of cognitive functioning.

In our study, there was no significant difference observed in the age of onset (F=1.49, p=0.23), whereas the difference observed in the duration of heroin consumption at different doses was significant (F=3.30, p=0.043). Impairment of recent memory, mental balance, attention and concentration, recognition, P/Kx100, and PQ was significantly associated with higher doses of heroin i.e. 2-3 gm as compared to 1-1.9 gm and 0-0.9 gm as $p<0.05$. There was no significant difference observed at different doses of heroin on the verbal adult intelligence scale, Nahor Benson test and Bender Gestalt test. Significant differences were found between 0-0.9 gm vs 1-1.9 gm and 0-0.9 gm vs 2-3.0 gm, suggesting that higher doses negatively impacted recent memory, mental balance, attention and concentration, recognition, P/KX100 giving higher dysfunction rating score as $p= <0.05$. The significant differences in cognitive functions and dysfunction rating scores at varying doses of heroin consumption are justified by the dose-dependent neurotoxic effects of heroin. Higher doses result in more severe neurochemical disruptions, leading to pronounced impairments in these domains [17,92,93]. The statistical analyses support these findings, highlighting the robust nature of the observed differences. The lack of significant differences in certain cognitive measures suggests variability in the sensitivity of these tests to heroin dose effects.

Ahmad, Ahmad, and Bindra (1989) [94] reported that heroin addicts performed worse than normal controls on tests of intelligence, memory, attention, concentration, and perceptual-motor coordination. Meta-analytical research indicates that chronic heroin use is linked to moderate deficits in verbal fluency, verbal working memory, inhibitory control, planning, and decision-making based on risk and reward [18]. Patients with active dependence exhibited significantly poorer verbal and visual working memory, verbal learning, sustained attention, psychomotor speed, and flexibility compared to abstinent patients and healthy controls [51,73]. Mitrović SM et al. [73] studied verbal memory in subjects, finding performance within average values for their age, with no significant

differences in heroin abuse duration (F=6.024; df=0.12). Heroin abuse has been shown to impair delayed visual memory [95], with effects observed after more than a year of use, consistent with Prosser's findings [96]. In contrast, Pathak et al. [97] found heroin abuse impacted the processing of visual information at the sensory memory level but not at deeper processing levels. Lee and Pau [98] demonstrated that former heroin users showed reckless behavior and poor problem-solving skills. Multiple studies have shown severe deficits in executive functions among heroin users, including intra-dimensional set-shifting, perseveration, risk-taking, and decision-making [29,99-101]. Korin (1974) [102] studied perceptual-motor disturbances among heroin addicts, concluding that such deficits were associated with heroin use. Heroin addicts made more errors on the Bender–Gestalt Test, which correlated with increased perseveration errors and limited use of space in their drawings compared to non-opiate addicts. Saroj R et al. [51] found that patients on buprenorphine and naltrexone exhibited limited but significant cognitive impairment, with the highest severity of neurocognitive impairment in those with active opioid dependence.

Subsequent neuroanatomical and neurofunctional studies suggested that grey matter atrophy in the medial and inferior prefrontal cortex, insula, and temporal cortex, along with abnormal activation of the rostral anterior cingulate cortex, underlie these executive dysfunctions in heroin users [103,104]. A recent systematic review concluded that heroin use is associated with weak fronto-cingulate connectivity with subcortical regions but strong functional connectivity with the amygdala and striatum [105]. Structural MRI studies have revealed grey matter and white matter reductions in the striatum, fronto-cortical and cingulate regions, and the amygdala and insula among heroin users [106-108].

In our study, age positively correlated with duration (rho= 0.53, p= <0.01) and dose (rho= 0.52, p= <0.01) of opioid use, suggesting older individuals had longer duration of opioid use and used higher doses. This can be

explained due to the cumulative exposure to opioids and the progression of dependency. Immediate memory improved slightly with increasing age (rho=-0.24, p=0.003) and use of higher doses (rho=-0.25, p=0.003). As older individuals may have a higher cognitive reserve, which can provide a protective effect against the cognitive impairments associated with opioid use [109-111]. This reserve might explain the slight improvement in immediate memory despite increased age and dose. Furthermore, Dose-Dependent Neuroplasticity, that is, in some cases, higher doses of opioids might temporarily enhance certain cognitive functions due to their complex interaction with brain neurochemistry, although this is not sustainable in the long term [112]. There were slight positive correlations between age, dose, and certain cognitive measures like recent memory and TQ arithmetic indicating that with an increase in age and dose of opioids, there was a slight worsening of scores on recent memory and TQ arithmetic. This can be attributed to the neurodegenerative effects of opioids or age-related cognitive decline. Age of onset also shows significant correlations with dose (rho= 0.22, p= 0.007) and immediate memory (rho= -0.19, p= 0.02), indicating the timing of onset of opioid use affects these variables. Overall, the findings underscore the complex interplay between the duration and dose of opioid use, age, and cognitive functions. They highlight the cumulative and progressive nature of opioid-related cognitive impairments, influenced by both the neurotoxic effects of opioids and natural age-related cognitive decline.

In natural opioid users, age was found to be negatively correlated with PQ-VQ and NBT, indicating that these measures tend to show a decrease in scores with increasing age. Natural age-related cognitive decline is compounded by opioid use, leading to lower PQ-VQ and NBT scores with increasing age. Age of onset among natural opioid users was negatively correlated with duration, suggesting that a later age of onset of opioid use was associated with a shorter duration of use. Individuals who start using opioids later have less time for prolonged use, resulting in a shorter

duration of use. The dose of natural opioids was positively correlated with duration and TQ Arithmetic, indicating higher doses are associated with longer durations of use and poor performance on TQ arithmetic. Longer and higher-dose opioid use leads to more significant cognitive impairments, particularly in tasks requiring sustained attention and calculation [113], such as TQ Arithmetic. Conversely, the dose was negatively correlated with immediate memory and TQ Comprehension scores, suggesting that higher doses may be associated with slight improvements in immediate memory and TQ Comprehension. In some cases, higher doses may slightly improve specific cognitive functions due to adaptive changes or increased cognitive reserve, reflected in better immediate memory and TQ Comprehension scores. These findings highlight the complex interplay between the duration and dose of opioid use, age of onset, and cognitive functions, emphasizing the need for targeted interventions considering these factors.

In synthetic opioid users, it was seen that there were significant positive correlations between age, age of onset, dose and duration of synthetic opioids with cognitive variables namely, PQ, NBT and dysfunction rating score as $p = <0.05$, indicating worsening of scores of these variables with increasing age, onset of opioid use at a later age, higher doses and longer duration of use. The cumulative neurotoxic effects of prolonged and high-dose synthetic opioid use led to the worsening of cognitive functions over time. Furthermore, age, age of onset and duration of use of synthetic opioids were positively correlated with attention and concentration and negatively correlated with immediate recall. Age and age of onset of synthetic opioid use were also positively correlated with recent memory and TQ arithmetic, indicating the worsening of scores of recent memory and TQ arithmetic with increasing age and a later age of onset. The natural decline in cognitive functions with age, combined with the additional burden of synthetic opioid use, leads to poorer performance in recent memory and TQ Arithmetic. Later onset may mean less overall

exposure but still results in significant impairment due to the combined effects of ageing and opioid toxicity. The age of the subjects and duration of use of synthetic opioids were positively correlated with visual retention and recognition. The cumulative impact of opioid use affects visual retention and recognition abilities, explaining the positive correlation with age and duration. The dissociation between the recognition process and the learning process is a key characteristic of frontal amnestic syndromes. This condition is marked by impaired learning abilities while recognition remains intact. This suggests that the verbal memory deficits observed in heroin addicts are likely of a frontal nature. [73,114]. Thus, the brain regions responsible for these functions are progressively damaged by long-term opioid exposure supporting our findings. Positive correlations were also found between age of onset and mental balance, duration and TQ information, and dose and P/KX100 and TQ digit span. Higher doses of synthetic opioids correlated with more pronounced impairments in mental balance, TQ Information, and TQ Digit Span. These cognitive domains are particularly vulnerable to the neurotoxic effects of opioids, which intensify with increased dosage and prolonged use. The variability in findings across studies on the cognitive effects of opioid use underscores the complex interplay of factors such as duration and dose of use, age of onset, neurotoxic effects, and individual differences in recovery. Understanding these nuances is crucial for interpreting the cognitive impacts of opioid use and for developing targeted interventions to support cognitive health in opioid-dependent individuals.

Our findings correlated with the study performed by Marwa Y. Badr et. al. [115] where there was no significant correlation between cognition and age(R=0.38, p=0.098), duration of heroin use(R=0.185, p=0.435) and dose of heroin(R=-0.193, p=0.416). This contrasts with the meta-regression findings by Wollman et al. [48], which did not find a relationship between the duration of opioid abuse and cognitive function. Conversely, a study by Mitrović SM et. al. [73] established a significant correlation

between short-term memory deficits and the overall duration of heroin abuse. The study also found that individuals with a longer duration of addiction typically began heroin use at a younger age (F4.716; df=0.012). Heroin abuse for more than a year resulted in statistically significant short-term verbal memory impairment, particularly in those who started using heroin early and experienced multiple interruptions in their substance abuse.

Some authors suggest that prolonged use of opioids causes detrimental effects on cognition which remains persistent. In 2013 McDonald et al. [116] conducted a study in which the opioid maintenance group exhibited poorer performance on verbal and non-verbal learning (immediate and delayed recall), executive function, processing speed and social perception and interaction than the control and abstinent group, although no significant difference was found. Darke et al. [117] conducted a study involving 125 older patients receiving maintenance treatment, 50 older users not receiving maintenance treatment, and 50 healthy controls. They found that executive functioning, information processing speed, and verbal learning were significantly impaired in patients undergoing maintenance treatment. However, there was no significant difference in cognitive performance between the older users not receiving maintenance treatment and the control group.

In various studies, the authors hypothesized that the brain of opioid users can self-repair, leading to improvements in cognitive functions over time. However, others have suggested that opioids cause lasting cognitive damage. There is no definitive evidence indicating which specific cognitive functions are most affected. Some studies proposed that memory was not significantly degraded whereas in numerous other studies, it was found to be impaired [21,22,29,30,118]. Previous meta-analyses and reviews have demonstrated that individuals with opioid dependence exhibit widespread cognitive impairments, impacting attention, working memory, impulsivity,

and decision-making [48,119]. However, the methodological variations among these studies make it challenging to generalize the findings.

SUMMARY AND CONCLUSION

It was a cross-sectional and comparative study that was conducted on 140 patients seeking treatment for Opioid Dependence to assess the cognition of opioid users and compare the cognition between natural opioid users and synthetic opioid users.

1. The majority of subjects used synthetic opioids (51.4%), with heroin being the most common (47.9%).
2. Most subjects with opioid dependence were under 30 years of age (46.4%). The mean age of natural opioid users was 36.32 ± 9.14 years, while synthetic opioid users averaged 30.25 ± 7.51 years.
3. Most subjects were married, but a larger proportion of synthetic opioid users were unmarried (48.6%). However, the difference between the two groups was not statistically significant.
4. The majority of subjects were literate and had completed up to secondary education (58%), with no significant difference observed between the types of opioids used.
5. Most subjects were employed. Those in skilled and semi-professional jobs predominantly used natural opioids, while unemployed subjects mainly used synthetic opioids, with a significant difference between the groups ($p < 0.001$).
6. The majority of subjects belonged to the upper middle class (57.4%) and lower middle class (43.1%), with natural opioids being more common in the former and synthetic opioids in the latter. There was no significant difference between the groups based on socioeconomic status.
7. Most subjects were from nuclear families, with a higher prevalence of synthetic opioid use (81.9%), demonstrating a significant difference between the groups ($p = 0.014$).
8. Synthetic opioid users began using opioids at an earlier age (Mean = 23.94, SD = 6.6) compared to natural opioid users (Mean = 26.47, SD = 8.16), with a significant difference ($p = 0.047$).

9. Natural opioids were used for a longer duration (Mean = 9.87, SD = 6.11) compared to synthetic opioids (Mean = 6.29, SD = 3.52), with a significant difference ($p < 0.001$).
10. Peer pressure (62.9%) was the most common precipitating factor for opioid use. Among natural opioid users, interpersonal issues (42.6%) also led to substance use, with a highly significant difference between the groups ($p < 0.001$).
11. Comorbid nicotine use was seen in 79.3% of users, predominantly among synthetic opioid users, with a significant difference ($p = 0.004$).
12. The majority of subjects did not have a family history of opioid dependence or mental illness, and the difference between the two groups was not significant.
13. Cognitive variables such as remote memory, recent memory, immediate recall, retention of similar pairs, retention of dissimilar pairs, TQ information, TQ comprehension, and PQ-VQ were relatively intact, with no significant difference between the groups.
14. Cognitive variables including mental balance, delayed recall, performance quotient, TQ digit span, TQ arithmetic, and Nahor Benson test were impaired in opioid users, with significant differences between the groups ($p < 0.05$).
15. Cognitive variables such as attention and concentration, visual retention, recognition, P/KX100, and Bender Gestalt test were impaired in opioid users, but the difference between the two groups was not significant.
16. Higher Dysfunction Rating Scores (>20) were significantly more common among synthetic opioid users (86.1%) compared to natural opioid users (60.3%).
17. The mean Dysfunction Rating Score was 21.91 ± 6.54 for natural opioid users and 25.25 ± 6.39 for synthetic opioid users, with the difference between the two groups being significant ($p = 0.003$).

18. The difference in the age of onset among different heroin dose groups was not significant ($p = 0.23$). However, the difference in the duration of use across the dose groups was significant ($p = 0.043$). Users with higher doses (2-3.0 gm) had a longer duration of use compared to those using lower doses (0-0.9 gm and 1-1.9 gm).
19. In heroin users, recent memory, mental balance, attention and concentration, recognition, P/Kx100, and PQ were significantly impacted at higher doses, having higher Dysfunction Rating Scores ($p < 0.05$).
20. Impairments in recent memory, mental balance, attention and concentration, recognition, P/Kx100, and higher Dysfunction Rating Scores were observed at higher doses of heroin (>1 gm) compared to lower doses (0-0.9 gm).
21. Among raw opium users, age and age of onset did not vary significantly with dose, while the duration of use was significantly affected by dose.
22. Cognitive variables such as attention and concentration, delayed recall, and Nahor Benson test were impaired and the magnitude of impairment was significant across different doses of raw opium.
23. Older individuals used higher doses of opioids for longer durations. A later age of onset was associated with higher doses. Immediate memory improved with increasing age and higher doses. Cognitive measures such as recent memory and TQ arithmetic were positively correlated with age and dose. Age of onset also showed significant correlations with dose and immediate memory, indicating the timing of onset affected these variables.
24. In natural opioid users, age was negatively correlated with PQ-VQ and NBT, indicating that these measures tend to improve with increasing age slightly. A later age of onset was associated with shorter duration. Dose was positively correlated with the duration and TQ arithmetic and the magnitude of impairment was significant. Dose

was negatively correlated with immediate memory indicating higher doses might improve immediate memory.

25. In synthetic opioid users, it was observed that there were significant positive correlations between age, age of onset, dose and duration of synthetic opioids with cognitive variables namely, PQ, NBT and dysfunction rating score as p= <0.05. Furthermore, age, age of onset and duration of use of synthetic opioids were positively correlated with attention and concentration and negatively correlated with immediate recall. Age and age of onset of synthetic opioid use were also positively correlated with recent memory and TQ arithmetic. The age of the subject and duration of use of synthetic opioids were positively correlated with visual retention and recognition. Positive correlations were also found between age of onset and mental balance, duration and TQ information, and dose and P/KX100 and TQ digit span.

CONCLUSION

Our study contributes valuable insight to the literature as there is limited research evaluating cognitive functions in opioid dependence. Due to the complexity of controlling all factors influencing cognitive functions in opioid dependence, further prospective studies are needed. Our findings indicate significant impairment in neurocognitive domains among opioid-dependent individuals, with synthetic opioid users exhibiting greater impairment compared to natural opioid users, and underscore the complex interplay of individual, social, and environmental factors influencing opioid use patterns. The overlapping nature of cognitive dysfunctions across various domains makes it challenging to determine which cognitive domain is most impacted or should be prioritised in cognitive rehabilitation approaches. These findings can inform the development of treatment strategies with targeted interventions and policies aimed at preventing relapse, maintaining abstinence, enhancing the effectiveness of treatment, and addressing the diverse needs of individuals affected by opioid-

dependent patients. Therefore, further studies are warranted in this area, especially in the Indian context.

LIMITATIONS

1. The small sample size of patients with opioid dependence in our study does not represent the total population of opioid-dependence patients. This limitation restricts the ability to generalize the results to the broader population.
2. The study was conducted in a tertiary care institute within the private sector, which may not reflect the conditions or patient demographics of other healthcare settings, including public hospitals or community clinics. This could influence the applicability of the findings to the general population.
3. Accurate quantification of the opioid dose was not feasible in this study. As a result, dosage information was based solely on the participants' self-reports and their estimations in grams. This reliance on self-reported data may introduce inaccuracies due to recall bias or misreporting.

These limitations should be taken into account when interpreting the results and considering the implications for broader clinical practice and future research.

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S NO.	MRD NUMBER	NAME INTIALS	TYPE OF SUBSTANCE	SUBSTANCE	AGE	GENDER	MARITAL STATUS	EDUCATION	OCCUPATION	SOCIOECONOMIC STATUS	FAMILY	AGE OF ONSET	DURATION
1	1660063	V	HEROIN	Synthetic	30	MALE	MARRIED	GRADUATE	PROFESSIONAL	UPPER	NUCLEAR	23	7
2	1545434	JS	TRAMADOL	Synthetic	30	MALE	MARRIED	SECONDARY	SKILLED	UPPER MIDDLE	NUCLEAR	28	2
3	1445883	HK	HEROIN	Synthetic	26	MALE	MARRIED	SECONDARY	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	20	6
4	1483699	SS	HEROIN	Synthetic	30	MALE	MARRIED	DIPLOMA	CLERK	UPPER MIDDLE	NUCLEAR	20	10
5	518711	GS	HEROIN	Synthetic	31	MALE	MARRIED	SECONDARY	UNEMPLOYED	UPPER MIDDLE	NUCLEAR	23	9
6	1480812	GG	RAW OPIUM	Natural	39	MALE	MARRIED	GRADUATE	PROFESSIONAL	UPPER MIDDLE	NUCLEAR	19	20
7	1516844	SS	RAW OPIUM	Natural	30	MALE	MARRIED	GRADUATE	PROFESSIONAL	UPPER	NUCLEAR	20	10
8	1502568	VB	HEROIN	Synthetic	25	MALE	UNMARRIED	GRADUATE	STUDENT	UPPER MIDDLE	NUCLEAR	18	7
9	1496921	VC	POPPY HUSK	Natural	33	MALE	UNMARRIED	DIPLOMA	SKILLED	LOWER MIDDLE	NUCLEAR	14	18
10	1490757	GS	POPPY HUSK	Natural	38	MALE	MARRIED	SECONDARY	SKILLED	UPPER LOWER	NUCLEAR	23	15
11	1264183	GS	HEROIN	Synthetic	27	MALE	UNMARRIED	SECONDARY	SKILLED	UPPER LOWER	NUCLEAR	21	6
12	1204525	IPS	RAW OPIUM	Natural	20	MALE	UNMARRIED	SECONDARY	UNEMPLOYED	UPPER MIDDLE	NUCLEAR	17	4
13	1553429	S	HEROIN	Synthetic	22	MALE	UNMARRIED	GRADUATE	UNEMPLOYED	UPPER LOWER	JOINT	20	2
14	1561660	LG	HEROIN	Synthetic	27	MALE	UNMARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER	NUCLEAR	19	8
15	1579998	LS	RAW OPIUM	Natural	26	MALE	MARRIED	GRADUATE	SKILLED	LOWER MIDDLE	JOINT	24	2
16	1252378	SS	RAW OPIUM	Natural	32	MALE	MARRIED	SECONDARY	SKILLED	LOWER MIDDLE	NUCLEAR	23	9
17	1566536	D	HEROIN	Synthetic	28	MALE	MARRIED	SECONDARY	CLERK	LOWER MIDDLE	NUCLEAR	13	15
18	1569530	NS	HEROIN	Synthetic	25	MALE	MARRIED	SECONDARY	UNEMPLOYED	UPPER LOWER	NUCLEAR	21	4
19	1588562	PS	RAW OPIUM	Natural	43	MALE	MARRIED	SECONDARY	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	26	17
20	1589892	AS	RAW OPIUM	Natural	27	MALE	UNMARRIED	POSTGRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	26	1
21	1662902	JS	HEROIN	Synthetic	31	MALE	MARRIED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	25	5
22	1369014	JS	HEROIN	Synthetic	21	MALE	UNMARRIED	SECONDARY	SKILLED	LOWER MIDDLE	NUCLEAR	19	2
23	1659123	AK	RAW OPIUM	Natural	33	MALE	MARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	30	3
24	1359777	CS	HEROIN	Synthetic	24	MALE	UNMARRIED	SECONDARY	UNEMPLOYED	UPPER LOWER	NUCLEAR	17	6
25	1660082	DS	RAW OPIUM	Natural	43	MALE	UNMARRIED	MIDDLE SCHOOL	SKILLED	UPPER MIDDLE	JOINT	25	18
26	1653402	GS	TRAMADOL	Synthetic	23	MALE	UNMARRIED	DIPLOMA	UNEMPLOYED	UPPER MIDDLE	NUCLEAR	20	3
27	1476734	HS	HEROIN	Synthetic	21	MALE	UNMARRIED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	17	4
28	1344438	HS	RAW OPIUM	Natural	27	MALE	MARRIED	GRADUATE	CLERK	UPPER MIDDLE	JOINT	18	10
29	1390405	GS	HEROIN	Synthetic	34	MALE	MARRIED	DIPLOMA	CLERK	LOWER MIDDLE	NUCLEAR	26	8
30	1465775	RS	RAW OPIUM	Natural	34	MALE	MARRIED	GRADUATE	SKILLED	UPPER MIDDLE	JOINT	26	8
31	1568038	GS	HEROIN	Synthetic	27	MALE	MARRIED	SECONDARY	SKILLED	UPPER LOWER	NUCLEAR	23	4
32	1482413	KS	HEROIN	Synthetic	33	MALE	UNMARRIED	SECONDARY	CLERK	LOWER MIDDLE	NUCLEAR	27	6
33	1041119	AKS	HEROIN	Synthetic	36	MALE	DIVORVCED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	JOINT	31	5
34	1663721	G	RAW OPIUM	Natural	39	MALE	MARRIED	SECONDARY	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	31	8
35	907136	SG	HEROIN	Synthetic	42	MALE	DIVORVCED	SECONDARY	UNEMPLOYED	UPPER MIDDLE	NUCLEAR	37	5
36	1667889	VS	HEROIN	Synthetic	40	MALE	MARRIED	HIGH SCHOOL	SKILLED	UPPER LOWER	NUCLEAR	27	13
37	1668957	SS	RAW OPIUM	Natural	27	MALE	UNMARRIED	SECONDARY	SKILLED	UPPER MIDDLE	LIVING ALONE	19	8
38	1669846	SS	HEROIN	Synthetic	34	MALE	UNMARRIED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	22	12
39	1674464	RK	HEROIN	Synthetic	49	MALE	MARRIED	HIGH SCHOOL	SKILLED	LOWER MIDDLE	NUCLEAR	39	10
40	1669613	JS	RAW OPIUM	Natural	32	MALE	UNMARRIED	GRADUATE	SKILLED	LOWER MIDDLE	NUCLEAR	26	6
41	1154605	GS	RAW OPIUM	Natural	34	MALE	DIVORVCED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	26	8

S NO.	MRD NUMBER	PRECIPITATING FACTOR	DOSE(GM)	COMORBID NICOTINE	FHO OPIOID DEPENDENCE	FHO MENTAL ILLNESS	REMOTE MEMORY	RECENT MEMORY	MENTAL BALANCE	ATTENTION AND CONCENTRATION	DELAYED RECALL	IMMEDIATE RECALL	RETENTION FOR SIMILAR PAIRS
1	1660063	PEER PRESSURE	3	YES	NO	NO	0	2	2	0	3	0	0
2	1545434	PEER PRESSURE	1	NO	NO	YES	2	2	2	3	3	0	0
3	1445883	PEER PRESSURE	0.5	YES	YES	NO	0	2	3	3	3	0	0
4	1483699	PEER PRESSURE	0.5	YES	NO	NO	2	0	2	0	2	0	0
5	518711	PEER PRESSURE	1	YES	NO	NO	0	2	3	3	2	2	2
6	1480812	PEER PRESSURE	12	YES	NO	NO	3	0	2	2	3	0	0
7	1516844	INTERPERSONAL ISSUE	10	YES	NO	NO	0	0	3	2	2	0	0
8	1502568	PEER PRESSURE	1	YES	NO	NO	0	2	0	2	3	0	0
9	1496921	PEER PRESSURE	300	YES	NO	NO	0	0	3	2	2	0	0
10	1490757	RECREATION	50	NO	YES	NO	2	2	3	3	2	0	0
11	1264183	PEER PRESSURE	1.5	YES	NO	NO	0	0	3	3	3	0	0
12	1204525	PEER PRESSURE	3	YES	NO	NO	0	0	3	2	3	0	0
13	1553429	RECREATION	1.5	YES	NO	NO	2	2	3	0	3	0	0
14	1561660	PEER PRESSURE	3	NO	YES	NO	0	0	2	3	3	2	0
15	1579998	INTERPERSONAL ISSUE	0.5	YES	NO	NO	2	2	3	2	2	0	0
16	1252378	PEER PRESSURE	10	YES	NO	NO	0	0	0	2	0	0	0
17	1566536	PEER PRESSURE	3	YES	NO	NO	0	0	3	2	2	2	0
18	1569530	PEER PRESSURE	0.5	YES	NO	NO	0	0	2	3	3	0	0
19	1588562	PEER PRESSURE	10	YES	NO	NO	2	0	0	0	3	0	0
20	1589892	PEER PRESSURE	3	NO	NO	NO	0	0	3	0	2	0	0
21	1662902	PEER PRESSURE	0.5	YES	NO	YES	0	0	3	2	3	0	0
22	1369014	PEER PRESSURE	0.5	YES	NO	NO	0	0	0	2	3	0	0
23	1659123	PEER PRESSURE	1	YES	NO	NO	0	2	0	0	3	2	0
24	1359777	PEER PRESSURE	2	YES	YES	NO	0	2	3	2	3	2	0
25	1660082	RECREATION	10	NO	NO	NO	0	2	0	0	3	0	3
26	1653402	PEER PRESSURE	1	YES	YES	YES	0	0	3	2	3	2	0
27	1476734	PEER PRESSURE	0.5	YES	NO	YES	0	0	2	0	3	0	0
28	1344438	PEER PRESSURE	2	YES	NO	NO	0	0	2	2	3	2	0
29	1390405	PEER PRESSURE	3	YES	NO	NO	0	2	3	2	3	0	0
30	1465775	PEER PRESSURE	3	YES	NO	NO	2	2	3	2	3	0	0
31	1568038	PEER PRESSURE	3	YES	NO	YES	0	0	3	2	3	0	0
32	1482413	PEER PRESSURE	3	YES	NO	NO	2	0	3	3	3	0	0
33	1041119	INTERPERSONAL ISSUE	2	YES	YES	NO	0	0	3	3	2	0	0
34	1663721	LONLINESS	4	NO	YES	NO	0	2	0	0	3	0	3
35	907136	LONLINESS	1.5	YES	NO	YES	0	2	3	3	2	0	0
36	1667889	PEER PRESSURE	2	NO	YES	NO	0	2	2	3	3	0	0
37	1668957	LONLINESS	1	YES	NO	NO	0	2	3	3	2	2	2
38	1669846	PEER PRESSURE	1	YES	NO	NO	0	2	3	3	3	0	0
39	1674464	INTERPERSONAL ISSUE	3	YES	NO	NO	0	2	3	3	3	0	0
40	1669613	PEER PRESSURE	8	YES	NO	NO	0	0	3	2	3	0	0
41	1154605	INTERPERSONAL ISSUE	5	YES	NO	NO	2	0	3	3	3	0	0

S NO.	MRD NUMBER	RETENTION FOR DISSIMILAR PAIRS	VISUAL RETENTION	RECOGNITION	P/KX100	PQ	TQ INFORMATION	TQ DIGIT SPAN	TQ ARITHMETIC	TQ COMPREHENSION	PQ-VQ	NBT	BGT	DYSFUNCTION RATING SCORE
1	1660063	0	0	0	0	0	0	0	0	0	0	0	3	10
2	1545434	3	3	2	3	2	3	0	2	2	0	2	3	37
3	1445883	2	3	3	3	0	0	0	3	0	0	2	3	30
4	1483699	2	2	2	3	2	0	0	0	0	3	2	3	25
5	518711	3	2	3	2	0	0	0	0	0	0	0	3	27
6	1480812	2	0	2	3	2	0	0	0	0	3	2	3	27
7	1516844	0	0	0	0	2	0	0	2	0	0	2	3	16
8	1502568	2	0	2	2	0	0	0	0	0	3	2	3	21
9	1496921	2	0	2	0	0	0	0	3	0	0	0	3	17
10	1490757	0	2	2	0	0	0	0	0	0	0	0	2	18
11	1264183	3	2	2	0	0	0	2	2	0	0	2	3	25
12	1204525	3	2	2	2	0	0	0	2	0	0	2	3	24
13	1553429	0	0	0	0	0	0	0	3	0	0	0	3	16
14	1561660	2	2	2	0	0	0	0	2	0	0	2	3	23
15	1579998	2	2	0	0	0	2	0	2	0	0	0	3	14
16	1252378	2	0	0	0	0	0	0	0	0	3	2	3	12
17	1566536	2	2	3	3	2	0	0	0	0	0	2	3	26
18	1569530	2	0	3	0	0	2	0	2	2	2	2	3	26
19	1588562	0	0	0	0	0	0	0	2	0	0	0	3	10
20	1589892	0	0	0	0	0	0	0	0	0	2	0	2	9
21	1662902	0	0	0	0	0	0	0	0	0	0	2	3	13
22	1369014	2	0	0	0	0	0	0	0	0	0	0	3	10
23	1659123	0	0	2	0	0	0	0	2	0	0	0	3	12
24	1359777	2	0	2	3	0	0	0	0	0	0	0	3	22
25	1660082	0	3	0	2	0	0	0	0	0	0	2	3	18
26	1653402	2	3	2	0	0	0	0	0	0	0	2	3	22
27	1476734	2	2	2	0	0	0	0	0	0	0	0	2	13
28	1344438	3	2	2	0	0	0	0	0	0	3	0	2	21
29	1390405	2	2	2	0	0	0	2	0	0	0	2	3	23
30	1465775	2	0	2	0	2	0	0	2	0	3	2	2	27
31	1568038	3	2	2	3	2	2	0	2	0	3	2	3	32
32	1482413	3	2	2	3	2	0	2	2	0	3	2	3	35
33	1041119	2	2	2	3	2	0	2	2	0	3	2	2	32
34	1663721	0	3	0	2	0	0	0	0	0	0	2	3	18
35	907136	2	0	3	2	2	0	0	2	0	0	3	3	27
36	1667889	2	3	2	2	2	0	0	2	0	0	3	3	29
37	1668957	3	2	3	2	0	0	0	0	0	0	0	3	27
38	1669846	2	3	3	3	0	0	0	3	0	0	0	3	28
39	1674464	2	3	3	3	0	0	0	3	0	0	2	3	30
40	1669613	3	2	2	3	2	2	0	2	0	3	2	3	32
41	1154605	3	2	2	3	2	0	2	2	0	3	2	3	35

S NO.	MRD NUMBER	NAME INTIALS	TYPE OF SUBSTANCE	SUBSTANCE	AGE	GENDER	MARITAL STATUS	EDUCATION	OCCUPATION	SOCIOECONOMIC STATUS	FAMILY	AGE OF ONSET	DURATION
42	1656629	KR	HEROIN	Synthetic	45	MALE	MARRIED	MIDDLE SCHOOL	SKILLED	LOWER MIDDLE	NUCLEAR	31	14
43	1640462	SS	RAW OPIUM	Natural	29	MALE	UNMARRIED	MIDDLE SCHOOL	SKILLED	LOWER MIDDLE	JOINT	18	11
44	1656400	BS	RAW OPIUM	Natural	55	MALE	MARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	47	8
45	1539665	HS	RAW OPIUM	Natural	41	MALE	MARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	33	8
46	1650648	AS	HEROIN	Synthetic	32	MALE	MARRIED	GRADUATE	SKILLED	LOWER MIDDLE	NUCLEAR	28	4
47	1655493	TS	RAW OPIUM	Natural	33	MALE	MARRIED	SECONDARY	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	31	2
48	1655203	CMM	POPPY HUSK	Natural	58	MALE	MARRIED	MIDDLE SCHOOL	ELEMENTARY	UPPER LOWER	NUCLEAR	46	12
49	1653064	BS	RAW OPIUM	Natural	50	MALE	MARRIED	HIGH SCHOOL	CLERK	LOWER MIDDLE	JOINT	35	15
50	1651090	SS	RAW OPIUM	Natural	36	MALE	MARRIED	MIDDLE SCHOOL	SKILLED	LOWER MIDDLE	NUCLEAR	20	16
51	987633	AS	POPPY HUSK	Natural	36	MALE	MARRIED	HIGH SCHOOL	SKILLED	LOWER MIDDLE	JOINT	34	2
52	1652283	PS	POPPY HUSK	Natural	50	MALE	DIVORVCED	HIGH SCHOOL	ELEMENTARY	UPPER LOWER	JOINT	30	20
53	1413920	S	HEROIN	Synthetic	23	MALE	UNMARRIED	GRADUATE	UNEMPLOYED	UPPER MIDDLE	JOINT	21	2
54	1412886	B	HEROIN	Synthetic	30	MALE	UNMARRIED	SECONDARY	SEMI-PROFESSIONAL	LOWER MIDDLE	NUCLEAR	27	3
55	1482840	PS	RAW OPIUM	Natural	46	MALE	MARRIED	SECONDARY	SKILLED	UPPER MIDDLE	NUCLEAR	41	5
56	1488426	HS	RAW OPIUM	Natural	30	MALE	UNMARRIED	SECONDARY	SKILLED	LOWER MIDDLE	NUCLEAR	15	15
57	502285	GK	RAW OPIUM	Natural	32	MALE	MARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	22	10
58	1522343	GS	HEROIN	Synthetic	29	MALE	MARRIED	GRADUATE	CLERK	UPPER MIDDLE	NUCLEAR	21	8
59	1528702	HS	RAW OPIUM	Natural	34	MALE	MARRIED	HIGH SCHOOL	SEMI-PROFESSIONAL	LOWER MIDDLE	NUCLEAR	18	16
60	1530128	HSM	RAW OPIUM	Natural	31	MALE	UNMARRIED	HIGH SCHOOL	SKILLED	LOWER MIDDLE	JOINT	17	14
61	612251	SC	RAW OPIUM	Natural	28	MALE	UNMARRIED	DIPLOMA	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	22	6
62	1530674	SS	HEROIN	Synthetic	23	MALE	UNMARRIED	GRADUATE	CLERK	UPPER MIDDLE	NUCLEAR	16	7
63	563836	SS	RAW OPIUM	Natural	47	MALE	MARRIED	DIPLOMA	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	22	25
64	1280682	PS	HEROIN	Synthetic	26	MALE	UNMARRIED	SECONDARY	SKILLED	LOWER MIDDLE	NUCLEAR	19	7
65	1320525	MS	HEROIN	Synthetic	27	MALE	MARRIED	SECONDARY	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	25	2
66	1534676	KS	HEROIN	Synthetic	31	MALE	UNMARRIED	SECONDARY	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	21	10
67	1442056	VV	HEROIN	Synthetic	29	MALE	UNMARRIED	SECONDARY	SEMI-PROFESSIONAL	LOWER MIDDLE	NUCLEAR	24	5
68	847398	JS	RAW OPIUM	Natural	49	MALE	MARRIED	GRADUATE	SKILLED	UPPER MIDDLE	NUCLEAR	29	20
69	1547296	GS	RAW OPIUM	Natural	31	MALE	UNMARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	LIVING ALONE	23	8
70	1678141	R	HEROIN	Synthetic	29	MALE	MARRIED	PRIMARY SCHOOL	UNEMPLOYED	UPPER LOWER	JOINT	25	4
71	1633663	LS	TRAMADOL	Synthetic	59	MALE	MARRIED	HIGH SCHOOL	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	51	8
72	1634648	SS	RAW OPIUM	Natural	22	MALE	UNMARRIED	SECONDARY	UNEMPLOYED	UPPER MIDDLE	NUCLEAR	17	5

S NO.	MRD NUMBER	PRECIPITATING FACTOR	DOSE(GM)	COMORBID NICOTINE	FHO OPIOID DEPENDENCE	FHO MENTAL ILLNESS	REMOTE MEMORY	RECENT MEMORY	MENTAL BALANCE	ATTENTION AND CONCENTRATION	DELAYED RECALL	IMMEDIATE RECALL	RETENTION FOR SIMILAR PAIRS
42	1656629	INTERPERSONAL ISSUE	2	YES	YES	YES	0	2	3	3	3	0	0
43	1640462	PEER PRESSURE	8	YES	NO	NO	2	0	2	0	2	0	0
44	1656400	INTERPERSONAL ISSUE	10	NO	NO	NO	0	2	3	3	2	2	2
45	1539665	INTERPERSONAL ISSUE	15	NO	YES	NO	3	0	2	2	3	0	0
46	1650648	PEER PRESSURE	2	YES	NO	NO	0	0	3	2	2	0	0
47	1655493	INTERPERSONAL ISSUE	5	NO	NO	YES	0	2	0	2	3	0	0
48	1655203	INTERPERSONAL ISSUE	100	YES	NO	NO	0	0	3	2	2	0	0
49	1653064	INTERPERSONAL ISSUE	9	NO	NO	NO	2	2	3	3	2	0	0
50	1651090	PEER PRESSURE	15	YES	NO	NO	0	0	3	3	3	0	0
51	987633	INTERPERSONAL ISSUE	80	NO	NO	NO	0	0	3	2	3	0	0
52	1652283	PEER PRESSURE	100	YES	YES	NO	2	2	3	0	3	0	0
53	1413920	PEER PRESSURE	2	NO	NO	NO	0	2	3	2	3	2	0
54	1412886	PEER PRESSURE	2	YES	NO	YES	0	2	3	3	2	2	2
55	1482840	INTERPERSONAL ISSUE	15	NO	NO	NO	0	0	0	2	3	0	0
56	1488426	RECREATION	2.5	YES	NO	NO	0	0	3	2	3	0	0
57	502285	INTERPERSONAL ISSUE	1.5	YES	NO	NO	0	2	3	3	2	2	2
58	1522343	PEER PRESSURE	3	YES	NO	NO	0	2	2	3	3	0	0
59	1528702	PEER PRESSURE	25	YES	NO	YES	0	2	3	3	2	2	2
60	1530128	PEER PRESSURE	20	YES	YES	YES	0	2	3	3	3	0	0
61	612251	INTERPERSONAL ISSUE	15	YES	NO	NO	0	2	3	3	3	0	0
62	1530674	INTERPERSONAL ISSUE	1.5	YES	NO	YES	0	2	3	3	2	2	2
63	563836	PEER PRESSURE	30	YES	NO	NO	0	2	3	3	3	0	0
64	1280682	PEER PRESSURE	3	YES	NO	NO	0	0	3	3	3	0	0
65	1320525	PEER PRESSURE	1	YES	NO	NO	0	2	3	3	2	2	2
66	1534676	PEER PRESSURE	3	YES	NO	NO	0	0	2	2	3	0	0
67	1442056	PEER PRESSURE	2	YES	NO	NO	0	0	2	2	3	0	0
68	847398	INTERPERSONAL ISSUE	30	YES	NO	NO	0	0	0	2	3	0	0
69	1547296	RECREATION	4	YES	NO	NO	0	2	2	0	2	0	0
70	1678141	PEER PRESSURE	1	NO	NO	NO	0	2	2	3	3	0	0
71	1633663	RECREATION	1	NO	NO	NO	0	2	3	2	3	0	0
72	1634648	PEER PRESSURE	5	YES	YES	YES	2	2	3	2	3	0	0

S NO.	MRD NUMBER	RETENTION FOR DISSIMILAR PAIRS	VISUAL RETENTION	RECOGNITION	P/KX100	PQ	TQ INFORMATION	TQ DIGIT SPAN	TQ ARITHMETIC	TQ COMPREHENSION	PQ-VQ	NBT	BGT	DYSFUNCTION RATING SCORE
42	1656629	2	3	3	2	2	0	0	2	0	0	3	3	31
43	1640462	2	2	2	3	2	0	0	0	0	3	2	3	25
44	1656400	3	2	3	2	0	0	0	0	0	0	0	3	27
45	1539665	2	0	2	3	2	0	0	0	0	3	2	3	27
46	1650648	0	0	0	0	2	0	0	2	0	0	2	3	16
47	1655493	2	0	2	2	0	0	0	0	0	3	2	3	21
48	1655203	2	0	2	0	0	0	0	3	0	0	0	3	17
49	1653064	0	2	2	0	0	0	0	0	0	0	0	2	18
50	1651090	3	2	2	0	0	0	2	2	0	0	2	3	25
51	987633	3	2	2	2	0	0	0	2	0	0	2	3	24
52	1652283	0	0	0	0	0	0	0	3	0	0	0	3	16
53	1413920	2	0	2	3	0	0	0	0	0	0	2	3	24
54	1412886	3	2	3	2	0	0	0	0	0	0	0	3	27
55	1482840	2	2	2	0	0	0	0	0	0	0	0	2	13
56	1488426	3	2	2	3	2	0	2	2	0	3	2	2	31
57	502285	3	2	3	2	0	0	0	0	0	0	0	3	27
58	1522343	2	3	2	2	2	0	0	2	0	0	3	3	29
59	1528702	3	2	3	2	0	0	0	0	0	0	0	3	27
60	1530128	2	3	3	3	0	0	0	3	0	0	0	3	28
61	612251	2	3	3	3	0	0	0	3	0	0	2	3	30
62	1530674	3	2	3	2	0	0	0	0	0	0	0	3	27
63	563836	2	3	3	3	0	0	0	3	0	0	0	3	28
64	1280682	3	2	2	3	2	0	2	2	0	3	2	3	33
65	1320525	3	2	3	2	0	0	0	0	0	0	0	3	27
66	1534676	3	2	3	3	0	0	0	0	0	2	2	2	24
67	1442056	2	0	2	3	2	0	0	0	0	3	2	2	23
68	847398	2	2	2	0	0	0	0	0	0	0	0	2	13
69	1547296	2	0	0	0	0	0	0	0	0	3	2	3	16
70	1678141	2	3	2	2	2	0	0	2	0	0	3	3	29
71	1633663	2	2	2	0	0	0	2	0	0	0	2	3	23
72	1634648	2	0	2	0	2	0	0	2	0	3	2	2	27

S NO.	MRD NUMBER	NAME INTIALS	TYPE OF SUBSTANCE	SUBSTANCE	AGE	GENDER	MARITAL STATUS	EDUCATION	OCCUPATION	SOCIOECONOMIC STATUS	FAMILY	AGE OF ONSET	DURATION
73	1626735	PM	HEROIN	Synthetic	34	MALE	MARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	32	2
74	1445885	AK	RAW OPIUM	Natural	32	MALE	MARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	24	8
75	1638785	HS	HEROIN	Synthetic	25	MALE	UNMARRIED	POSTGRADUATE	UNEMPLOYED	UPPER MIDDLE	NUCLEAR	24	1
76	1639406	VJ	RAW OPIUM	Natural	24	MALE	UNMARRIED	GRADUATE	UNEMPLOYED	UPPER MIDDLE	JOINT	19	5
77	1217671	SSP	HEROIN	Synthetic	29	MALE	MARRIED	SECONDARY	SKILLED	UPPER MIDDLE	NUCLEAR	23	6
78	1632715	E	HEROIN	Synthetic	20	MALE	UNMARRIED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	17	3
79	1612015	GS	HEROIN	Synthetic	27	MALE	UNMARRIED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	22	5
80	1531159	AS	RAW OPIUM	Natural	23	MALE	MARRIED	SECONDARY	UNEMPLOYED	UPPER MIDDLE	NUCLEAR	21	2
81	681825	MS	HEROIN	Synthetic	25	MALE	MARRIED	SECONDARY	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	19	6
82	1519838	PS	HEROIN	Synthetic	25	MALE	UNMARRIED	DIPLOMA	UNEMPLOYED	UPPER MIDDLE	NUCLEAR	17	8
83	817326	PS	RAW OPIUM	Natural	27	MALE	UNMARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	24	3
84	1553881	GSB	RAW OPIUM	Natural	27	MALE	MARRIED	GRADUATE	SKILLED	UPPER MIDDLE	NUCLEAR	26	1
85	1521754	HS	POPPY HUSK	Natural	30	MALE	UNMARRIED	GRADUATE	SKILLED	LOWER MIDDLE	NUCLEAR	23	7
86	1486575	RS	RAW OPIUM	Natural	29	MALE	UNMARRIED	SECONDARY	SKILLED	UPPER MIDDLE	NUCLEAR	22	7
87	1379848	VK	HEROIN	Synthetic	32	MALE	UNMARRIED	MIDDLE SCHOOL	ELEMENTARY	UPPER LOWER	NUCLEAR	29	3
88	1623186	PS	RAW OPIUM	Natural	49	MALE	MARRIED	SECONDARY	SKILLED	LOWER MIDDLE	NUCLEAR	45	4
89	1514946	HS	HEROIN	Synthetic	26	MALE	UNMARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	21	5
90	425691	AT	RAW OPIUM	Natural	40	MALE	MARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	26	14
91	1306950	IS	RAW OPIUM	Natural	30	MALE	MARRIED	GRADUATE	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	24	6
92	1526037	PC	HEROIN	Synthetic	21	MALE	UNMARRIED	DIPLOMA	UNEMPLOYED	UPPER MIDDLE	NUCLEAR	19	2
93	1594310	RS	HEROIN	Synthetic	40	MALE	MARRIED	SECONDARY	SKILLED	UPPER MIDDLE	NUCLEAR	36	4
94	1216851	AS	RAW OPIUM	Natural	42	MALE	MARRIED	SECONDARY	SKILLED	LOWER MIDDLE	NUCLEAR	36	6
95	1300277	HS	RAW OPIUM	Natural	43	MALE	MARRIED	SECONDARY	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	26	17
96	889747	RS	RAW OPIUM	Natural	27	MALE	UNMARRIED	POSTGRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	26	1
97	1317845	V	HEROIN	Synthetic	30	MALE	MARRIED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	25	5
98	1652832	RS	HEROIN	Synthetic	21	MALE	UNMARRIED	SECONDARY	SKILLED	LOWER MIDDLE	NUCLEAR	19	2
99	1219671	SS	HEROIN	Synthetic	33	MALE	MARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	30	3
100	1660864	BS	HEROIN	Synthetic	23	MALE	UNMARRIED	SECONDARY	UNEMPLOYED	UPPER LOWER	NUCLEAR	17	6
101	1663195	GS	RAW OPIUM	Natural	43	MALE	UNMARRIED	MIDDLE SCHOOL	SKILLED	UPPER MIDDLE	JOINT	25	18
102	960122	JS	TRAMADOL	Synthetic	23	MALE	UNMARRIED	DIPLOMA	UNEMPLOYED	UPPER MIDDLE	NUCLEAR	20	3
103	1657397	AK	HEROIN	Synthetic	21	MALE	UNMARRIED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	17	4
104	1507915	KS	HEROIN	Synthetic	28	MALE	MARRIED	GRADUATE	CLERK	UPPER MIDDLE	JOINT	18	10
105	1659240	KV	HEROIN	Synthetic	34	MALE	MARRIED	DIPLOMA	CLERK	LOWER MIDDLE	NUCLEAR	26	8
106	31620	PK	HEROIN	Synthetic	34	MALE	MARRIED	GRADUATE	SKILLED	UPPER MIDDLE	JOINT	26	8
107	1636214	RS	HEROIN	Synthetic	27	MALE	MARRIED	SECONDARY	SKILLED	UPPER LOWER	NUCLEAR	23	4
108	1682655	KS	HEROIN	Synthetic	33	MALE	UNMARRIED	SECONDARY	CLERK	LOWER MIDDLE	NUCLEAR	27	6

S NO.	MRD NUMBER	PRECIPITATING FACTOR	DOSE(GM)	COMORBID NICOTINE	FHO OPIOID DEPENDENCE	FHO MENTAL ILLNESS	REMOTE MEMORY	RECENT MEMORY	MENTAL BALANCE	ATTENTION AND CONCENTRATION	DELAYED RECALL	IMMEDIATE RECALL	RETENTION FOR SIMILAR PAIRS
73	1626735	PEER PRESSURE	1	YES	NO	YES	0	0	3	2	3	0	0
74	1445885	PEER PRESSURE	10	YES	YES	NO	0	0	3	2	2	0	0
75	1638785	INTERPERSONAL ISSUE	0.5	YES	NO	YES	0	0	2	2	3	2	0
76	1639406	INTERPERSONAL ISSUE	0.5	YES	NO	YES	0	2	3	2	3	0	0
77	1217671	PEER PRESSURE	2	YES	NO	NO	0	2	3	3	2	3	2
78	1632715	PEER PRESSURE	2	YES	NO	YES	0	2	2	2	3	2	0
79	1612015	PEER PRESSURE	1.5	YES	NO	NO	0	2	3	3	3	0	0
80	1531159	PEER PRESSURE	2	YES	NO	NO	2	0	3	2	3	0	0
81	681825	PEER PRESSURE	2	YES	NO	NO	0	0	3	2	3	2	0
82	1519838	PEER PRESSURE	3	YES	NO	NO	0	0	2	3	3	0	0
83	817326	PEER PRESSURE	2.5	YES	NO	NO	0	0	2	2	3	0	0
84	1553881	PEER PRESSURE	15	YES	NO	YES	0	0	2	2	3	0	0
85	1521754	INTERPERSONAL ISSUE	70	YES	NO	NO	0	0	0	2	3	0	0
86	1486575	PEER PRESSURE	10	YES	YES	YES	0	2	2	0	2	0	0
87	1379848	PEER PRESSURE	2	YES	NO	NO	0	2	2	3	3	0	0
88	1623186	INTERPERSONAL ISSUE	8	NO	NO	NO	0	2	3	3	2	2	2
89	1514946	PEER PRESSURE	3	YES	NO	NO	0	2	3	3	3	0	0
90	425691	INTERPERSONAL ISSUE	3	NO	NO	NO	0	2	3	3	3	0	0
91	1306950	INTERPERSONAL ISSUE	10	YES	NO	NO	0	0	0	2	3	2	0
92	1526037	PEER PRESSURE	1	YES	NO	NO	0	0	3	2	2	2	0
93	1594310	PEER PRESSURE	2	YES	NO	NO	0	2	2	2	3	2	0
94	1216851	INTERPERSONAL ISSUE	10	YES	NO	NO	0	2	3	3	3	0	0
95	1300277	PEER PRESSURE	10	YES	NO	NO	2	0	0	0	3	0	0
96	889747	PEER PRESSURE	3	NO	NO	NO	0	0	3	0	2	0	0
97	1317845	PEER PRESSURE	0.5	YES	NO	YES	0	0	3	2	3	0	0
98	1652832	PEER PRESSURE	0.5	YES	NO	NO	0	0	0	2	3	0	0
99	1219671	PEER PRESSURE	1	YES	NO	NO	0	2	0	0	3	2	0
100	1660864	PEER PRESSURE	2	YES	YES	NO	0	2	3	2	3	2	0
101	1663195	RECREATION	10	NO	NO	NO	0	2	0	0	3	0	3
102	960122	PEER PRESSURE	1	YES	YES	YES	0	0	3	2	3	2	0
103	1657397	PEER PRESSURE	0.5	YES	NO	YES	0	0	2	0	3	0	0
104	1507915	PEER PRESSURE	2	YES	NO	NO	0	0	2	2	3	2	0
105	1659240	PEER PRESSURE	3	YES	NO	NO	0	2	3	2	3	0	0
106	31620	PEER PRESSURE	3	YES	NO	NO	2	2	3	2	3	0	0
107	1636214	PEER PRESSURE	3	YES	NO	YES	0	0	3	2	3	0	0
108	1682655	PEER PRESSURE	3	YES	NO	NO	2	0	3	3	3	0	0

S NO.	MRD NUMBER	RETENTION FOR DISSIMILAR PAIRS	VISUAL RETENTION	RECOGNITION	P/KX100	PQ	TQ INFORMATION	TQ DIGIT SPAN	TQ ARITHMETIC	TQ COMPREHENSION	PQ-VQ	NBT	BGT	DYSFUNCTION RATING SCORE
73	1626735	3	2	2	3	2	2	0	2	0	3	2	3	32
74	1445885	2	0	2	0	0	0	0	3	0	0	0	3	17
75	1638785	3	2	2	0	0	0	0	0	0	3	0	2	21
76	1639406	2	2	2	0	0	0	2	0	0	0	2	3	23
77	1217671	3	2	0	2	0	0	0	0	0	0	0	3	25
78	1632715	3	3	2	0	0	0	0	0	0	3	2	3	27
79	1612015	2	3	3	3	0	0	0	3	0	0	2	3	30
80	1531159	2	3	2	2	0	0	0	0	0	0	2	2	23
81	681825	2	2	2	0	0	0	0	0	0	0	2	3	21
82	1519838	2	2	2	3	2	0	2	2	0	3	2	3	31
83	817326	3	2	3	3	0	0	0	0	0	2	2	2	24
84	1553881	2	0	2	3	2	0	0	0	0	3	2	2	23
85	1521754	2	2	2	0	0	0	0	0	0	0	0	2	13
86	1486575	2	0	0	0	0	0	0	0	0	3	2	3	16
87	1379848	2	3	2	2	2	0	0	2	0	0	3	3	29
88	1623186	3	2	3	2	0	0	0	0	0	0	0	3	27
89	1514946	2	3	3	3	0	0	0	3	0	0	0	3	28
90	425691	2	3	3	3	0	0	0	3	0	0	2	3	30
91	1306950	3	2	2	0	0	0	0	0	0	0	0	3	17
92	1526037	2	2	2	0	0	0	0	2	0	0	2	2	21
93	1594310	3	3	2	0	0	0	0	0	0	3	2	3	27
94	1216851	2	3	3	3	0	0	0	3	0	0	2	3	30
95	1300277	0	0	0	0	0	0	0	2	0	0	0	3	10
96	889747	0	0	0	0	0	0	0	0	0	2	0	2	9
97	1317845	0	0	0	0	0	0	0	0	0	0	2	3	13
98	1652832	2	0	0	0	0	0	0	0	0	0	0	3	10
99	1219671	0	0	2	0	0	0	0	2	0	0	0	3	12
100	1660864	2	0	2	3	0	0	0	0	0	0	0	3	22
101	1663195	0	3	0	2	0	0	0	0	0	0	2	3	18
102	960122	2	3	2	0	0	0	0	0	0	0	2	3	22
103	1657397	2	2	2	0	0	0	0	0	0	0	0	2	13
104	1507915	3	2	2	0	0	0	0	0	0	3	0	2	21
105	1659240	2	2	2	0	0	0	2	0	0	0	2	3	23
106	31620	2	0	2	0	2	0	0	2	0	3	2	2	27
107	1636214	3	2	2	3	2	2	0	2	0	3	2	3	32
108	1682655	3	2	2	3	2	0	2	2	0	3	2	3	35

S NO.	MRD NUMBER	NAME INTIALS	TYPE OF SUBSTANCE	SUBSTANCE	AGE	GENDER	MARITAL STATUS	EDUCATION	OCCUPATION	SOCIOECONOMIC STATUS	FAMILY	AGE OF ONSET	DURATION
109	1219386	CS	HEROIN	Synthetic	36	MALE	DIVORVCED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	JOINT	31	5
110	1673583	SS	RAW OPIUM	Natural	39	MALE	MARRIED	SECONDARY	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	31	8
111	1683523	SS	HEROIN	Synthetic	42	MALE	DIVORVCED	SECONDARY	UNEMPLOYED	UPPER MIDDLE	NUCLEAR	37	5
112	1439871	HS	HEROIN	Synthetic	40	MALE	MARRIED	HIGH SCHOOL	SKILLED	UPPER LOWER	NUCLEAR	27	13
113	1681143	JS	RAW OPIUM	Natural	27	MALE	UNMARRIED	SECONDARY	SKILLED	UPPER MIDDLE	LIVING ALONE	19	8
114	1683502	NS	HEROIN	Synthetic	34	MALE	UNMARRIED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	22	12
115	404483	PS	HEROIN	Synthetic	49	MALE	MARRIED	HIGH SCHOOL	SKILLED	LOWER MIDDLE	NUCLEAR	39	10
116	1674462	PS	RAW OPIUM	Natural	32	MALE	UNMARRIED	GRADUATE	SKILLED	LOWER MIDDLE	NUCLEAR	26	6
117	72277	VK	RAW OPIUM	Natural	34	MALE	DIVORVCED	SECONDARY	UNEMPLOYED	LOWER MIDDLE	NUCLEAR	26	8
118	1195605	NS	HEROIN	Synthetic	45	MALE	MARRIED	MIDDLE SCHOOL	SKILLED	LOWER MIDDLE	NUCLEAR	31	14
119	1229704	SK	TRAMADOL	Synthetic	29	MALE	UNMARRIED	MIDDLE SCHOOL	SKILLED	LOWER MIDDLE	JOINT	18	11
120	1530245	PK	RAW OPIUM	Natural	55	MALE	MARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	47	8
121	1640804	BS	RAW OPIUM	Natural	41	MALE	MARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	JOINT	33	8
122	1743298	SS	HEROIN	Synthetic	32	MALE	MARRIED	GRADUATE	SKILLED	LOWER MIDDLE	NUCLEAR	28	4
123	1747168	HK	RAW OPIUM	Natural	33	MALE	MARRIED	SECONDARY	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	31	2
124	1743110	I	POPPY HUSK	Natural	58	MALE	MARRIED	MIDDLE SCHOOL	ELEMENTARY	UPPER LOWER	NUCLEAR	46	12
125	1749237	RM	RAW OPIUM	Natural	50	MALE	MARRIED	HIGH SCHOOL	CLERK	LOWER MIDDLE	JOINT	35	15
126	503324	RK	RAW OPIUM	Natural	36	MALE	MARRIED	MIDDLE SCHOOL	SKILLED	LOWER MIDDLE	NUCLEAR	20	16
127	1733880	SS	POPPY HUSK	Natural	36	MALE	MARRIED	HIGH SCHOOL	SKILLED	LOWER MIDDLE	JOINT	34	2
128	1749896	GS	POPPY HUSK	Natural	50	MALE	DIVORVCED	HIGH SCHOOL	ELEMENTARY	UPPER LOWER	JOINT	30	20
129	283770	MS	HEROIN	Synthetic	23	MALE	UNMARRIED	GRADUATE	UNEMPLOYED	UPPER MIDDLE	JOINT	21	2
130	1749504	RS	HEROIN	Synthetic	30	MALE	UNMARRIED	SECONDARY	SEMI-PROFESSIONAL	LOWER MIDDLE	NUCLEAR	27	3
131	1674706	MK	RAW OPIUM	Natural	46	MALE	MARRIED	SECONDARY	SKILLED	UPPER MIDDLE	NUCLEAR	41	5
132	1744670	SS	HEROIN	Synthetic	30	MALE	UNMARRIED	SECONDARY	SKILLED	LOWER MIDDLE	NUCLEAR	15	15
133	1729888	HSB	RAW OPIUM	Natural	32	MALE	MARRIED	GRADUATE	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	22	10
134	134809	GS	HEROIN	Synthetic	29	MALE	MARRIED	GRADUATE	CLERK	UPPER MIDDLE	NUCLEAR	21	8
135	1755207	NS	RAW OPIUM	Natural	34	MALE	MARRIED	HIGH SCHOOL	SEMI-PROFESSIONAL	LOWER MIDDLE	NUCLEAR	18	16
136	1454580	PK	RAW OPIUM	Natural	31	MALE	UNMARRIED	HIGH SCHOOL	SKILLED	LOWER MIDDLE	JOINT	17	14
137	1753012	BS	RAW OPIUM	Natural	28	MALE	UNMARRIED	DIPLOMA	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	22	6
138	1653458	BS	HEROIN	Synthetic	23	MALE	UNMARRIED	GRADUATE	CLERK	UPPER MIDDLE	NUCLEAR	16	7
139	1656313	RS	RAW OPIUM	Natural	47	MALE	MARRIED	DIPLOMA	SEMI-PROFESSIONAL	UPPER MIDDLE	NUCLEAR	22	25
140	1754104	AG	HEROIN	Synthetic	26	MALE	UNMARRIED	SECONDARY	SKILLED	LOWER MIDDLE	NUCLEAR	19	7

S NO.	MRD NUMBER	PRECIPITATING FACTOR	DOSE(GM)	COMORBID NICOTINE	FHO OPIOID DEPENDENCE	FHO MENTAL ILLNESS	REMOTE MEMORY	RECENT MEMORY	MENTAL BALANCE	ATTENTION AND CONCENTRATION	DELAYED RECALL	IMMEDIATE RECALL	RETENTION FOR SIMILAR PAIRS
109	1219386	INTERPERSONAL ISSUE	2	YES	YES	NO	0	0	3	3	2	0	0
110	1673583	LONLINESS	4	NO	YES	NO	0	0	3	2	2	0	0
111	1683523	LONLINESS	1.5	YES	NO	YES	0	2	3	3	2	0	0
112	1439871	PEER PRESSURE	2	NO	YES	NO	0	2	2	3	3	0	0
113	1681143	LONLINESS	1	YES	NO	NO	0	2	3	3	2	2	2
114	1683502	PEER PRESSURE	1	YES	NO	NO	0	2	3	3	3	0	0
115	404483	INTERPERSONAL ISSUE	3	YES	NO	NO	0	2	3	3	3	0	0
116	1674462	PEER PRESSURE	8	YES	NO	NO	0	0	3	2	2	0	0
117	72277	INTERPERSONAL ISSUE	5	YES	NO	NO	0	0	3	2	2	0	0
118	1195605	INTERPERSONAL ISSUE	2	YES	YES	YES	0	2	3	3	3	0	0
119	1229704	PEER PRESSURE	1	YES	NO	NO	0	2	2	3	3	0	0
120	1530245	INTERPERSONAL ISSUE	10	NO	NO	NO	0	2	3	3	2	2	2
121	1640804	INTERPERSONAL ISSUE	15	NO	YES	NO	0	2	3	3	3	0	0
122	1743298	PEER PRESSURE	2	YES	NO	NO	0	2	3	3	3	0	0
123	1747168	INTERPERSONAL ISSUE	5	NO	NO	YES	0	0	2	2	3	0	0
124	1743110	INTERPERSONAL ISSUE	100	YES	NO	NO	0	0	2	2	3	0	0
125	1749237	INTERPERSONAL ISSUE	9	NO	NO	NO	0	0	0	2	3	0	0
126	503324	PEER PRESSURE	15	YES	NO	NO	0	2	2	0	2	0	0
127	1733880	INTERPERSONAL ISSUE	80	NO	NO	NO	0	2	2	3	3	0	0
128	1749896	PEER PRESSURE	100	YES	YES	NO	0	2	3	3	3	0	0
129	283770	PEER PRESSURE	2	NO	NO	NO	0	2	3	2	3	2	0
130	1749504	PEER PRESSURE	2	YES	NO	YES	0	2	3	3	2	2	2
131	1674706	INTERPERSONAL ISSUE	15	NO	NO	NO	0	2	3	3	3	0	0
132	1744670	RECREATION	2.5	YES	NO	NO	0	0	3	2	3	0	0
133	1729888	INTERPERSONAL ISSUE	1.5	YES	NO	NO	0	2	3	3	2	2	2
134	134809	PEER PRESSURE	3	YES	NO	NO	0	2	2	3	3	0	0
135	1755207	PEER PRESSURE	25	YES	NO	YES	0	2	3	3	2	2	2
136	1454580	PEER PRESSURE	20	YES	YES	YES	0	2	3	3	3	0	0
137	1753012	INTERPERSONAL ISSUE	15	YES	NO	NO	0	2	3	3	3	0	0
138	1653458	INTERPERSONAL ISSUE	1.5	YES	NO	YES	0	2	0	2	3	0	0
139	1656313	PEER PRESSURE	30	YES	NO	NO	0	0	3	2	2	0	0
140	1754104	PEER PRESSURE	3	YES	NO	NO	0	0	3	3	3	0	0

S NO.	MRD NUMBER	RETENTION FOR DISSIMILAR PAIRS	VISUAL RETENTION	RECOGNITION	P/KX100	PQ	TQ INFORMATION	TQ DIGIT SPAN	TQ ARITHMETIC	TQ COMPREHENSION	PQ-VQ	NBT	BGT	DYSFUNCTION RATING SCORE
109	1219386	2	2	2	3	2	0	2	2	0	3	2	2	32
110	1673583	2	0	2	0	0	0	0	3	0	0	0	3	17
111	1683523	2	0	3	2	2	0	0	2	0	0	3	3	27
112	1439871	2	3	2	2	2	0	0	2	0	0	3	3	29
113	1681143	3	2	3	2	0	0	0	0	0	0	0	3	27
114	1683502	2	3	3	3	0	0	0	3	0	0	0	3	28
115	404483	2	3	3	3	0	0	0	3	0	0	2	3	30
116	1674462	2	0	2	0	0	0	0	3	0	0	0	3	24
117	72277	2	0	2	0	0	0	0	3	0	0	0	3	21
118	1195605	2	3	3	2	2	0	0	2	0	0	3	3	31
119	1229704	2	3	2	2	2	0	0	2	0	0	3	3	29
120	1530245	3	2	3	2	0	0	0	0	0	0	0	3	27
121	1640804	2	3	3	3	0	0	0	3	0	0	0	3	28
122	1743298	2	3	3	3	0	0	0	3	0	0	2	3	30
123	1747168	3	2	3	3	0	0	0	0	0	2	2	2	24
124	1743110	2	0	2	3	2	0	0	0	0	3	2	2	23
125	1749237	2	2	2	0	0	0	0	0	0	0	0	2	13
126	503324	2	0	0	0	0	0	0	0	0	3	2	3	16
127	1733880	2	3	2	2	2	0	0	2	0	0	3	3	29
128	1749896	2	3	3	3	0	0	0	3	0	0	0	3	30
129	283770	2	0	2	3	0	0	0	0	0	0	2	3	24
130	1749504	3	2	3	2	0	0	0	0	0	0	0	3	27
131	1674706	2	3	3	3	0	0	0	3	0	0	0	3	25
132	1744670	3	2	2	3	2	0	2	2	0	3	2	2	31
133	1729888	3	2	3	2	0	0	0	0	0	0	0	3	27
134	134809	2	3	2	2	2	0	0	2	0	0	3	3	29
135	1755207	3	2	3	2	0	0	0	0	0	0	0	3	27
136	1454580	2	3	3	3	0	0	0	3	0	0	0	3	28
137	1753012	2	3	3	3	0	0	0	3	0	0	2	3	30
138	1653458	2	0	2	2	0	0	0	0	0	3	2	3	21
139	1656313	2	0	2	0	0	0	0	3	0	0	0	3	17
140	1754104	3	2	2	3	2	0	2	2	0	3	2	3	33

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Subject:: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 25.09.2023 has approved the plan of thesis of **Alisha Aluna**, a student of your college for **MD Psychiatry** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
A comparative study to assess cognitive impairment among natural and synthetic opioid users .

Supervisor
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The student may submit the thesis in triplicate alongwith the plan in triplicate also, to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She may be directed to attach a photocopy of this letter with the forwarding letter while submitting thesis in the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic, if any.

Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*

A COMPARITIVE STUDY TO ASSESS COGNITIVE IMPAIRMENT AMONG NATURAL AND SYNTHETIC OPIOID USERS

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MD

In

PSYCHIATRY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

AUGUST, 2022

Dr. ALISHA ALUNA

DEPARTMENT OF PSYCHIATRY
DAYANAND MEDICAL COLLEGE AND HOSPITAL
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ABSTRACT OF PLAN OF THESIS

Title	A COMPARATIVE STUDY TO ASSESS COGNITIVE IMPAIRMENT AMONG NATURAL AND SYNTHETIC OPIOID USERS
For the degree of	M.D Psychiatry
Name of the candidate	Dr. Alisha Aluna
Supervisor	Dr. Pankaj Kumar, Associate Professor, Department of Psychiatry, Dayanand Medical College & Hospital
Co-supervisor(s)	Dr. Ranjive Mahajan, Professor and Head, Department of Psychiatry, Dayanand Medical College & Hospital, Ludhiana
Institution	Dayanand Medical College and Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Opioid Dependence is the major contributor to the global disease burden. Cognitive impairment is commonly seen in these patients. The study will be performed to determine the effect of opioids on the cognitive functions among the natural and synthetic opioid users. A cross sectional study will be performed which will compare the cognitive impairment occurring in patients consuming natural and synthetic opioid users.

Aim of Study: 1. To study the effects of opioid on cognitive function.
2. To compare the cognitive impairment among the groups- natural and synthetic opioid users.

Materials & methods: The study will be conducted on patients in the age group between 18-60 years diagnosed with opioid dependence as per ICD-11 criteria presenting to Deaddiction Centre/ Deaddiciton OPD, Department of Psychiatry, DMC&H Ludhiana during the period of one year. Patients will be assessed using neurophysiological test- PGIBBD

Clinical Significance: In this study cognitive functions of patients diagnosed with opioid dependence consuming natural and synthetic opioids would be assessed. Cognitive functioning play an important role in the course and prognosis of patients and would contribute to better understanding of cognitive symptoms as a part of comprehensive treatment strategies.

Keywords: Cognitive functions, Opioid dependence, Natural opioids, Synthetic opioids, PGIBBD

(Signature) Candidate	(Signature) Co-supervisor	(Signature) Supervisor	(Signature) Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"A COMPARATIVE STUDY TO ASSESS COGNITIVE IMPAIRMENT AMONG NATURAL AND SYNTHETIC OPIOID USERS"** exist in the Department of Psychiatry, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate herself under our supervision and guidance.

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4	DATE OF ADMISSION OF COURSE	07/03/2022
5	TITLE OF THE TOPIC	A COMPARITIVE STUDY TO ASSESS COGNITIVE IMPAIRMENT AMONG THE NATURAL AND SYNTHETIC OPIOID USERS

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Opioids are one of the most commonly used drugs that have been part of human existence for thousand of years. These are the group of analgesic agents that are derived from the Papaver somniferum. They act on the 3 classical opioid receptors in the body namely mu receptor/MOP, delta receptor/DOP and kappa receptor/KOP with novel NOP receptor which is considered to be a non opioid branch of opioid receptor family. Opioids act as agonists, antagonists and partial agonists on these receptors. Opioids may also be classified according to their mode of synthesis into Natural (Morphine, Codeine, Papaverine) which are the alkaloids derived from the resin of the poppy and Synthetic (Heroin, Buprenorphine, Oxycodone, Tramadol, Tapentadol, Fentanyl) which are chemically synthesized from the natural alkaloids of opium. All opioids which are used in clinical practice exert their action commonly on MOP receptors with additional activity on other opioid receptors or receptors distinct from opioid family[1].

Opioids have analgesic and sedative effects due to their action on MOP receptors, therefore they are commonly used for the management of pain. Opioids can cause reduction in consciousness and result in euphoria, which is one of the main reasons for their non-medical use. Regular non-medical use, prolonged use, misuse and use without medical supervision of opioids can lead to opioid dependence and other health problems. Opioid dependence is a disorder of regulation of opioid use arising from repeated or continuous use of opioids[2].

Opioid dependence is a substantial contributor to the global disease burden[3]. In 2019, nearly 62 million people were estimated to be past-year users of opioids, corresponding to 1.2 per cent of the global population aged 15–64[4]. The major rise in the global number of opioid users in recent years have been seen from Asia and Africa. For South Asia estimates have been revised upward, mainly owing to the availability of new estimates from India; the increase in Africa is attributed to more robust estimates from Nigeria in 2019[4].

In India, 2.1 per cent of the population aged 10–75, a total of 23 million people, were known to be past-year opioid users in 2018. The opioid with the highest prevalence of use was heroin with a past-year prevalence of 1.1 per cent among the population aged 10–75 years followed by the non-medical use of pharmaceutical opioids, the prevalence of which reached almost 1 per cent of the general population and opium, the prevalence of which was almost 0.5 percent[4]. In a study of Punjab opioid dependence survey, the AIIMS finding translated to 837 opioid dependents per 100,000 people in Punjab, or 0.84 percent of the state's 28 million population[5].

Opioids exert direct and indirect effects on cognitive processes[6]. While acute intake of opioids can impair some cognitive functions but these effects do not persist for long. Long term use of opioids may have long lasting effects among individuals with opioid use disorder. In a meta-analysis, chronic opioid exposure was mainly associated with cognitive deficits in verbal working memory, cognitive impulsivity (risk taking) and cognitive flexibility (verbal fluency)[7]. In general, human cognitive processes includes the knowledge of the mechanisms which determine the way how humans acquire information from the environment and utilize their knowledge and experience. There are three basic processes of human perception development: acquiring sensations, perceptiveness and attention. Mental processes of the higher order used in cognition with which humans try to understand the world and adapt to it include the processes of memory, reasoning, learning and problem solving. Human cognitive functions determine individuals' adaptation capabilities and disturbances in this area indicate a number of psychopathological changes and are a symptom enabling to differentiate or diagnose one with a disorder[8].

They also exert effects on the respiratory system-reducing respiratory rate and obtunding airway reflexes, an effect which is considered advantageous during anesthesia[1]. Although opioids are known to preserve cardiac stability, histamine release and the associated reductions in systemic vascular resistance with blood pressure are marked with morphine. Among other side-effects, opioids can cause

constipation, nausea, vomiting, urinary retention, pruritus, muscular rigidity, miosis and dysphoria in certain individuals[1].

A very few studies have been conducted in Indian scenario comparing the effect of opioids on cognition. As per the knowledge of the investigator few studies have been conducted which compared the two groups of opioids and their effect on cognition. Thus, in this study, we will determine whether opioid use is associated with cognitive impairment. The comparison would be done in terms of cognitive impairment among the natural and synthetic opioid users.

6.2 REVIEW OF LITERATURE

Opioids have been known in the history for their role as analgesics by acting on the opioid receptors present in the central and peripheral nervous system. Within the central nervous system, it is thought that major mechanism of opioid-induced analgesia is by activation of MOP receptors in the midbrain. Here, MOP agonists act by indirectly activating the descending inhibitory pathways through the action on the periaqueductal grey (PAG) and nucleus reticularis paragigantocellularis (NRPG). This causes greater neuronal traffic through the nucleus raphe magnus (NRM) which leads to increased stimulation of 5-hydroxytryptamine and enkephalin-containing neurons which connect directly with the substantia gelatinosa of the dorsal horn in turn leading to a reduction of nociceptive transmission from the periphery to the thalamus. Exogenous and endogenous opioids can also exert a direct inhibitory effect upon the substantia gelatinosa (in the dorsal horn) and peripheral nociceptive afferent neurons, reducing nociceptive transmission from the periphery[1].

Opioid's action on the mesolimbic (midbrain) reward system is the main cause for the occurrence of dependence. This reward system stimulates the ventral tegmental area (VTA) that causes the release of the chemical dopamine (DA) in the nucleus accumbens(NAc). This release of DA into the NAc causes feelings of pleasure. Many areas of the brain create a lasting memory that associate these good feelings with the circumstances and environment in which they occur. These memories are called conditioned associations which lead to the craving for drugs when the abuser re-encounters those circumstances and environment that causes the abusers to seek out more drugs. Particularly in the early stages of abuse, the opioid's stimulation of the brain's reward system is a primary reason that some people take drugs repeatedly[1]. The compulsion to use opioids develops gradually extending beyond a limit to achieve pleasure. This increased compulsion leads to tolerance and dependence.

Opioid dependence and the distressing opioid withdrawal symptoms arises from the area at the base of the brain—the locus ceruleus (LC).

Neurons in the LC produce noradrenaline (NA) which stimulates wakefulness, breathing, blood pressure, general alertness including other functions. When opioids bind to MOP receptors in LC, they suppress NA release from neurons resulting in drowsiness, slowed respiration, low blood pressure—effects similar to opioid intoxication. However with repeated exposure to opioids the LC neurons adjust by increasing their level of activity. Therefore when opioids are present, their suppressive impact is offset by this heightened activity, with the result that almost normal amounts of NA are released and the patient feels comparatively normal. Whereas when opioids are not present to suppress the LC neurons, they release excessive amounts of NA causing jitters, anxiety, muscle cramps, and diarrhea.

Between 2010 and 2019, the estimated number of opioid users worldwide nearly doubled from 31 million to almost 62 million estimated past-year users. At the same time, the prevalence of opioid use increased by 76 per cent and the global population increased by 10 per cent[4]. In India, 2.1 per cent of the population aged 10–75, a total of 23 million people, were estimated to be past-year opioid users in 2018. The opioid with the highest prevalence of use was heroin with a past-year prevalence of 1.1 per cent among the population aged 10–75 followed by the non-medical use of pharmaceutical opioids, the prevalence of which reached almost 1 per cent of the general population and opium, the prevalence of which was almost 0.5 per cent. Among the 23 million past year opioid users, 7.7 million were estimated to suffer from opioid use disorders[4].

One study was conducted by Ajit Avasthi et. al. entitled “Epidemiology of Substance Abuse and Dependence in the state of Punjab (India)” showed that 1.6% population aged 11-60 years residing in Punjab have been dependent on any substance in their lifetime. 1 in 120 of the source population is currently dependent on opioid and estimated no. of dependent persons is 0.17 million[9]. According to survey conducted by all India Institute and SPYM (Society for Promotion of youth and masses) in collaboration with NDDTC AIIMS, the no. of addicts in the state of Punjab is between 2.32 Lakh and was hooked to opioids.

61.6% and 1 in 4 were using injectable Opioids (Heroin), one third were abusing Buprenorphine. Most common cause of starting abuse of opioid was Fun (69.9%) followed by peer pressure (43.9%)[5]. In PODS (Punjab Opioid Dependence Survey), there are 837 opioid dependents per 100,000 people in Punjab, or 0.84 percent of the state's 28 million population out of which 33% were injecting drug users. Reason for starting drug abuse was peer influence in 75%, and 80% ever tried to quit and 35% ever received any help for quitting. Estimated number of opioid dependent in punjab = 2,32, 856. Among those 76% are in the age group (18-35yrs)[10].

ICD-11 gives the criteria for diagnosis of opioid dependence. It states that the characteristic feature is the strong internal drive to use opioids, which is manifested by impaired ability to control use, increasing priority given to use over other activities and persistence of use despite harm or negative consequences. These experiences are often accompanied by a subjective sensation of urge or craving to use opioids. Physiological features of dependence may also be present, including tolerance to the effects of opioids, withdrawal symptoms following cessation or reduction in use of opioids, or repeated use of opioids or pharmacologically similar substances to prevent or alleviate withdrawal symptoms. The features of dependence are usually evident over a period of at least 12 months but the diagnosis may be made if opioid use is continuous (daily or almost daily) for at least 1 month[2].

Opioid dependence leads to various complications in the form of medical, social and cognitive processes. Medical complications includes its effects on the respiratory system-reducing respiratory rate and obtunding airway reflexes, an effect which is considered advantageous during anaesthesia. Though opioids are considered to preserve cardiac stability, histamine release and the associated reductions in systemic vascular resistance and blood pressure are marked with morphine. Opioids can cause constipation, nausea, vomiting, urinary retention, pruritus, muscular rigidity, miosis and dysphoria in certain individuals. There is marked impact of opioids in

dependent subjects disrupting their life socially. The rates of dissatisfaction with life are higher among opioid-dependent persons as compared to the general population[11.] The QOL is severely impaired among opioid-dependent subjects[12.] Studies on QoL have recently started to involve the field of drug addiction to go beyond the presence and severity of addiction symptoms and the side effects of treatments by examining how drug-addicted patients perceive and experience the repercussions on their daily life[13].

Prolonged opioid use have significant impact on the cognitive processes. The cognitive deficits model of drug addiction proposes that individuals who develop addictive disorders have abnormalities in the prefrontal cortex (PFC). The PFC plays important role for regulation of judgment, planning, and other executive functions. To help us overcome some of our impulses for immediate gratification in favor of more important or ultimately more rewarding long-term goals, the PFC sends inhibitory signals to the VTA DA neurons of the mesolimbic reward system[14].

The cognitive deficits model proposes that PFC signaling to the mesolimbic reward system is compromised in individuals with addictive disorders, and as a result they have reduced ability to use judgment to restrain their impulses and are predisposed to compulsive drug-taking behaviors[15]. Stimulant drugs such as methamphetamine appear to damage the specific brain circuit—the frontostriatal loop—that carries inhibitory signals from the PFC to the mesolimbic reward system. The cognitive deficits model of drug addiction could explain the clinical observation that heroin addiction is more severe in individuals with antisocial personality disorder—a condition that is independently associated with PFC deficits[16]. Heroin causes damage to the PFC but not to the frontostriatal loop. Therefore, individuals who become heroin addicts may have some PFC damage that is independent of their opioid abuse, either inherited genetically or caused by some other factor or event in their lives. This preexisting PFC damage predisposes these individuals to impulsivity and lack of control, and the additional

PFC damage from chronic repeated heroin abuse increases the severity of these problems[17].

In a study conducted by Javier A. Tamargo it was seen that people who use opioids, the frequency of cognitive impairment was higher among those who used heroin or fentanyl than those who used prescription opioids. No difference was observed between people who used prescription opioids and people who did not use opioids. In univariate logistic regression, use of heroin was significantly associated with 2.59 times the odds for cognitive impairment than opioid non users. There was also a trend for cognitive impairment in association with fentanyl use[18].

Ornstein et. al.(2000) provided a profile of cognitive dysfunction among 22 men who used opiates regularly, mainly heroin, for at least 3 years and met the diagnostic criteria for opioid dependence. These individuals showed impairments in verbal fluency learning, spatial working memory, strategic performance and visual pattern recognition[19].

In a study conducted at Netherlands it was found that among the people with substance use disorder prevalence of cognitive impairments was 31% with prevalence of 34% for alcohol, 38% for opioids, 21% for cannabis and 27% for stimulants. Patients who were using opioids performed significantly worse on the visuospatial abilities and memory function with significant main effect found on executive functioning[20].

In a study on cognitive impairment and tramadol dependence it was seen that tramadol abuse patients were about 3 times more likely to have cognitive impairment than control subjects (81% vs 28%). Tramadol alone patients were twice more likely to have cognitive impairment than control subjects (67% vs 28%). Memory, visuospatial skills and verbal fluency was most affected amongst all cognitive domains[21].

6.3 AIMS AND OBJECTIVES OF THE STUDY

1. To study the effects of opioid on cognitive functions.

2. To compare the cognitive impairment among the groups- natural and synthetic opioid users

7. MATERIALS AND METHODS

7.1 Source of Data

Study will be conducted on patients diagnosed with Opioid Dependence Syndrome presenting to Deaddiction Centre/Deaddiction OPD, Department of Psychiatry, Dayanand Medical College & Hospital, Ludhiana

7.2 METHOD OF COLLECTION OF DATA

Sample collection: This is a comparative and cross sectional study design in which the study will be performed on patients seeking treatment for Opioid Dependence presenting to Deaddiction Centre/Deaddiction OPD, Department of Psychiatry, Dayanand Medical College & Hospital, Ludhiana during the period of 1 year with patient group divided into 2: one group who use natural opioids and second group who use synthetic opioids.

Patients

Inclusion criteria

1. Participants fulfilling Opioid Dependence Criteria as per ICD-11.
2. Using opioid for the minimum period of 12 months.
3. Age between 18-60 years.
4. Willing to give informed consent for participation.

Exclusion criteria

1. Intellectual disability, major psychiatric illnesses, neurological illness or head injury that limit the validity of cognitive test.
2. Meeting criteria for use of other substance (excluding nicotine).

In order to avoid additional bias, participants who would report using opioids as prescribed will not be included in this analysis.

Methodology

The study will be conducted on patients in age group of 18-60 years diagnosed with Opioid Dependence presenting to Deaddiction centre/Deaddiction OPD, Department of Psychiatry, DMC&H, Ludhiana during the period of one year with one group of patients using natural opioids and other group using synthetic opioids. To be eligible patients

have to meet the inclusion criteria and give written informed consent before enrollment. Their cognitive function will be assessed using the following neuropsychological assessment tests.

Instruments

A validated cognitive instrument will be administered as a part of the intake procedure that contains items covering all cognitive domains, PGIBBD(Post Graduate Institute Battery of Brain Dysfunction). This test battery attempts to evolve a psychometric profile that can differentiate patients of organic brain dysfunction from those having no organic pathology. This battery of tests was formulated by Pershad and Verma in 1990 to measure cognitive functions of the brain-behavior, namely intelligence (both verbal and performance), memory, perceptual acuity

and transference from one hemisphere to another. It is based on reception, consolidation (search) and execution of stimulations. It was standardized on adult males and females in the age group of 20-59 years of age. It measures the functioning of the brain and is not intended to be used for brain pathology lateralization or localization of hemispheric functions. It consists of PGI-Memory Scale, Battery of Performance Tests of Intelligence, Verbal Adult Intelligence Scale, Nahor-Benson Test and Bender Visual-Motor Gestalt Test. It takes nearly 90 to 120 minutes for its complete administration.

a. PGI-Memory Scale (PGIMS): This scale includes verbal and non-verbal material and measures remote, recent and immediate, short term, very short term very short-term intermediate term and long-term memories. There are 10 subtests, standardized on adult subjects in the age range of 20 to 45 years. Its test-retest reliability over a period of a week ranges from .69 to .85 for 10 subtests (N=40) and for the total test about 0.90 (test-retest and split half). Correlation of PGIMS with Boston's Memory Scale and Weschler's Memory Scale were found to be .71 and .85 respectively. It had significantly high correlation with education and low correlation with IQ. It has satisfactory cross-validity and provides quintile norms and a profile. Separate norms are provided

for three educational levels, i.e. ‘0 to 5’, ‘6 to 9’ and ’10 and above’ years of schooling (Pershad, 1977;Pershad and Wig, 1976, 1988)

b. Revised Bhatia’s Short Battery of Performance Tests of Intelligence(SB-R): This is an adaptation of Bhatia’s Battery of Performance Tests of Intelligence (Bhatia, 1955) Short Scale (Murthy, 1966) consisting of Koh’s Block Design and Alexander’s Pass-A-Long tests. This short scale was standardized on adult, healthy subjects in the age range of 20-59 years. Scoring was modified, norms were developed for 4 age groups, 3 educational levels separately for male and female to increase sensitivity of the scores. It gives Test Quotients (TQ) for two sub-tests which allow comparability of functions measured by Kohs’ Block Design Test and Pass-A-Long test. TQs of Kohs’ Block and Pass-A-Long tests were found to be significantly correlated with the IQs on Verbal Adult Intelligence Scale, Wechsler’s Adult Performance Intelligence Scale and Standard Progressive Matrices. Distribution of IQ formed a normal probability curve. Elderly subjects and subjects with low education obtained significantly low scores.(Pershad, Mahajan and Verma, 1988)

c. Verbal Adult Intelligence Scale (VAIS): This battery of Verbal Tests of Intelligence includes four sub-tests (1) Information (2) Digit Span (3)

Arithmetic and (4) Comprehension. To develop the items for these subtests, help was sought from Wechsler’s Adult Intelligence Scale. Pass percentages of the items were determined for different educational groups of adult subjects. The scores on information digit span arithmetic

comprehension and total score was correlated with Bhatia’s Short Scale,

Standard Progressive Matrices, Stanford Binet, Wechsler’s Performance

scale and WAIS-R. Scores on all the four subjects tend to increase with increase in education. This test battery provides norms for three

educational levels, and five age groups separately for males and females. It uses concept of Test Quotient (TQ) for determining level of

performance on each of the four sub-tests and mean of 4 TQs is Verbal Quotient (VQ). It does not take into account the speed or quickness, rather it emphasizes the power other capacity of the subjects. (Pershad and Verma, 1978)

d. Nahor-Benson Test (NBT): Nahor and Benson (1970) had developed a quick and simple screening test for organic brain pathology. A retrospective study was conducted at PGIMER, Chandigarh to find out the screening capacity and to ascertain the claims of utility of the authors about this test. It was found that the cases who were diagnosed as brain

dysfunction on follow-up had reproduced and made the drawings incorrect in sufficiently large number of cases compared to not brain dysfunction cases. Nearly 90% of the patients in non-brain dysfunction made errors on two or less drawings whereas in brain dysfunction group, 75% of the subjects made more than two errors. Age of the adult subjects was not found to be associated with the number of errors on this test (r=0.08) but education had a little significant but negative correlation (-0.47). Correlation of errors on this test with that of PQ and VQ were .27 and .45 respectively. (Pershad and Verma, 1978)

e. Bender Visual Motor Gestalt Test (Bender Gestalt Test) (BVMGT):

Based on Wertheimer's classical work in the field of perception, the

Bender Gestalt test was introduced by Bender in 1938. Various surveys

conducted in India and elsewhere to find out the 10 most frequently used

tests revealed that Bender Gestalt test occupied between 1st to 5th position at the top. The nine drawings to be copied therein, are simple and nonthreatening to the subjects. Various errors in the copying of the drawings were more frequently seen in the subjects with brain dysfunction then in non-brain dysfunction cases. Orientation of the presented paper for copying the design had a little influence on the performance of the subjects. (Verma, 1974)

OUTCOME

In this study, cognitive functions in patients with opioid dependence will be assessed and the comparison will be made between the natural and the synthetic opioid users. The present study will suggest that there is impairment of cognitive functions in patients with opioid dependence and the impairment of cognitive functions is more in synthetic opioid users as compared to those with natural opioid users. This would help determine the course and prognosis of the opioid dependence patients.

STATISTICAL ANALYSIS

Data will be described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data is normally distributed, a Kolmogorov-Smirnov test will be used. Comparison of quantitative variables between the study groups will be done using Student t-test and Mann Whitney U test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test will be performed and fisher exact test will be used when the expected frequency is less than 5. A probability value (p value) less than 0.05 will be considered statistically significant. All statistical calculations will be done using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

Urine for 10-P.

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Yes, Attached herewith.

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PROFORMA

S. No.

DATE:

NAME: AGE: GENDER:

MRD NO.:

MARITAL STATUS:

EDUCATION:

OCCUPATION:

LOSS OF FUNCTION:

INCOME:

TYPE OF FAMILY: JOINT/NUCLEAR/LIVING ALONE

ADDRESS:

CONTACT NO.:

AGE OF ONSET OF OPIOID DEPENDENCE:

DURATION OF ILLNESS /COURSE OF ILLNESS:

PRECIPITATING FACTOR

NUMBER AND TYPE OF SUBSTANCE CONSUMED:

INSIGHT GRADE:

COMORBID NICOTINE USE:

FAMILY HISTORY OF OPIOID DEPENDENCE

FAMILY HISTORY OF ANY MENTAL ILLNESS EXCEPT OPIOID DEPENDENCE

Signature of Candidate **Signature of Supervisor**

URINE FOR 10-P:

PGI BATTERY OF BRAIN DYSFUNCTION

1. REMOTE MEMORY:
2. RECENT MEMORY:
3. MENTAL BALANCE:
4. ATTENTION AND CONCENTRATION:
5. DELAYED RECALL:
6. IMMEDIATE RECALL:
7. RETENTION FOR SIMILAR PAIRS:
8. RETENTION FOR DISSIMILAR PAIRS:
9. VISUAL RETENTION:
10. RECOGNITION:
11. P/K x 100
12. PERFORMANCE QUOTIENT:
13. T.Q. ON INFORMATION:
14. T.Q. ON DIGIT SPAN:
15. T.Q ON ARITHMETIC:
16. T.Q. ON COMPREHENSION:
17. DIFFERENCE ON P.Q. AND V.Q.:
18. NAHOR BENSON TEST:
19. BENDER GESTALT TEST:

DYSFUNCTION RATING SCORE:

Signature of Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I……..D/o, W/o, S/o……. am willing to participate in the study **"A COMPARATIVE STUDY TO ASSESS COGNITIVE IMPAIRMENT AMONG NATURAL AND SYNTHETIC OPIOID USERS"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

……. ……

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"A COMPARATIVE STUDY TO ASSESS COGNITIVE IMPAIRMENT AMONG NATURAL AND SYNTHETIC OPIOID USERS"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____	_____
गवाह के हस्ताक्षर	रोगी के हस्ताक्षर/अंगूठे का निशान
नाम:	नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

“A COMPARATIVE STUDY TO ASSESS COGNITIVE IMPAIRMENT AMONG NATURAL AND SYNTHETIC OPIOID USERS” ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ